

# The effect of Mepitel Film on skin reaction severity in patients undergoing radiation therapy for head and neck cancer: a feasibility study

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**Hayley Wooding**

2016

A thesis submitted for the degree of Bachelor of Radiation Therapy with Honours at the University of  
Otago, Dunedin, New Zealand

## Abstract

Radiation skin reactions are a common side effect of radiation therapy and can be distressing and painful for patients. Head and neck cancer patients receive a high dose of radiation to the skin and are therefore at high risk of acute skin toxicity. There have been many clinical trials investigating topical agents to reduce or prevent these reactions but the evidence to date is lacking and many centres still base their practice on anecdotal evidence. Recently clinical trials in breast cancer patients have shown that using Mepitel Film® (Mölnlycke Health Care AB, Gothenburg, Sweden) reduced skin reaction severity and stopped the development of moist desquamation when used prophylactically (from the first day of radiation therapy). Mepitel Film and other soft silicone dressings that adhere very closely to the folds of the skin, have been hypothesized to decrease skin reaction severity by stopping friction by clothing and allow the radiation damaged skin to repair itself.

The aim of this randomised controlled feasibility study in this thesis was to investigate whether Mepitel Film dressings were superior to Sorbolene cream in reducing or managing radiation-induced skin reactions in patients with head and neck cancer. Head and neck cancer patients are prescribed a higher dose than breast cancer patients, have an uneven surface for the Mepitel Film to adhere to and have complex non-homogenous dose distributions. This means that testing the effect of Mepitel Film in this cohort would be challenging. Despite this, it was hypothesised that Mepitel Film was superior to standard Sorbolene cream in decreasing the severity of acute radiation-induced skin reaction in patients receiving radiation therapy for head and neck cancer.

In order to test this hypothesis a randomised, controlled, multi-centre, international, open label intra-patient feasibility study was conducted in New Zealand and China. This thesis analyses a subset of 12 patients recruited at the Canterbury Regional Cancer and Haematology Service (CRCHS) at Christchurch Public Hospital. For the first six patients, the study area was chosen as the area of first erythema which was divided into equal halves. Each half was randomised to either Mepitel Film or Sorbolene cream. Mepitel Film was applied as soon as erythema was visible (management protocol). For the next six patients, the study area was chosen at the planning stage to include an area of relatively uniform high dose (>40Gy). This area was divided into two equal halves; one half was randomised to Mepitel Film the other half to Sorbolene cream. Mepitel Film was applied from day one of radiation therapy treatment (prophylactic protocol). Sorbolene cream was applied twice a day by the patient. The Modified Radiation-induced Skin Reaction Assessment Scale (RISRAS) and the Modified Radiation Therapy Oncology Group (RTOG) skin toxicity score were used to assess skin

reaction severity three times a week. Patients also filled out the New Zealand validated Distress screening tool once a week and completed exit questionnaires at the end of the follow-up period. Thermoluminescent dosimeters (TLDs) were used to measure the actual dose to the skin underneath Mepitel Film and the control cream for all patients.

When results of all 12 patients were combined, there was a statistically significant decrease in skin reaction severity in favour of Mepitel Film of 29% for combined scores, of 15% for researcher scores and of 49% for patients' scores ( $p=0.001$ ,  $0.002$  and  $0.004$  respectively). The difference in peak RISRAS score between skin covered with Mepitel Film and control skin covered in cream was also significantly lower ( $p=0.02$ ). The results were disappointing compared to those reported by the breast cancer trial where skin reaction severity was reduced by more than 90% when Mepitel Film was used prophylactically. Several factors may explain the lack of effectiveness of the Mepitel Film in this patient cohort. Dose to the skin was significantly higher in head and neck cancer patients and Mepitel Film did not adhere well to skin with heavy beard stubble, which meant Mepitel Film needed to be replaced almost daily for the first few weeks of radiation therapy. The latter may also explain why there was no difference in the Mepitel Film effect between the skin of patients on the management protocol and those on the prophylactic protocol which should have had the strongest skin protective effect. In addition, compared with skin covering the breast area, skin in the neck area may be "tougher" and less likely to benefit from "friction protection".

The results suggest that Mepitel Film does reduce skin reaction severity in head and neck cancer patients but the increase in skin folds, beard growth and high skin dose mean that the protective effects of Mepitel Film are limited, particularly in men with heavy beard growth. Mepitel Film appeared to be more effective in women but there were too few women in this trial to perform a statistically meaningful analysis. Future research should include clinical studies in different cohorts of head and neck patients, such as in women and men with less beard growth.

## Acknowledgments

It is a pleasure to thank the many people who made this trial and thesis possible.

Firstly I would like to thank all of the patients who committed their time and energy to participate in this study. I enjoyed spending time with you and appreciated your willingness to have 'gladwrap on your face'. I also appreciate the extra appointments you made the effort to attend after you finished your radiation therapy, especially when that was often when you were feeling your worst.

Thank you to all the staff at the Canterbury Regional Cancer and Haematology Service for your patience and support. I am very grateful to Dr Iain Ward, for all your help. I also wish to thank Dr Avtar Raina and Dr Chris Harrington for supporting this research on your patients. Thank you to the research nurses for your willingness to offer your help with a smile, and to Maree Johnston who helped recruit patients into the trial. I also wish to thank Kate Dekker and Yasmin Mcquinlan for your assistance with the patient assessments when I was on leave. I am also thankful to Rob Hallinan and Phil Daly who allowed me time away from clinical work.

I offer my humble thanks to my supervisor Dr Ptries Herst for her tireless help, enthusiasm and encouragement. Without you running this trial would have been a daunting experience but you made it so easy and were so helpful with everything.

I also wish to thank my husband Sam for his support during the last two years.

I am very grateful to those who provided financial assistance towards the trial or my course fees. This includes:

- The Christchurch Oncology Trust Fund
- The University of Otago Research Fund

Finally, I wish to thank Mölnlycke Health Care for providing all of the Mepitel Film free of charge; without your generous donation this trial would not have been possible.

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## Chapter 1 Introduction

Cancer of the head and neck applies to mucosal cancers of the oral cavity and lip, pharynx, larynx and cervical oesophagus (1). It also includes the nasal cavity, paranasal sinuses and salivary glands (1). Rapid increases in the incidence of oral pharyngeal cancers have been found in both Australia and New Zealand, attributed largely to increased rates of Human Papilloma Virus in the population (2). Standard treatment for early or locally advanced cancers commonly include radiation therapy, as well as chemotherapy for those with high risk features (3).

Radiation-induced skin reactions occur commonly in everyday practice and are therefore important to consider when caring for oncology patients (4). Radiation reactions are a complex injury and can occur at the entry or exit point of the radiation beam (5). Radiation-induced skin reactions can occur in up to 90% of breast and head and neck cancer patients and although the incidence of moist desquamation overall can be low, it can be distressing and painful for the patients (6). Skin toxicity during treatment while distressing for the patient can also result in treatment delays in severe cases which can negatively impact the overall treatment (7).

Recent systematic reviews of the literature have shown a lack of strong evidence, in the form of randomised controlled clinical trials (RCTs), to support the use of any topical agent in reducing the incidence or severity of radiation-induced skin reactions (7,8). Due to this lack of evidence there is considerable variation in practice across Australasia, with 50% of centres reporting their skin care policy was based on anecdotal evidence (9).

A recent RCT conducted in New Zealand demonstrated the efficacy of Mepitel Film in significantly decreasing skin reaction severity for breast cancer patients by 90%, by reducing friction and trauma to the irradiated skin (10). Head and neck cancer patients pose a particular challenge for the use of dressings, due to the change in contour over the neck, facial hair and the higher dose of radiation prescribed to this patient group compared to breast cancer patients.

In order to test the effectiveness of Mepitel Film on head and neck cancer patients, a multi-centre, international, open-label, randomised, intra-individual comparison of Mepitel Film dressings versus Sorbolene Cream during radiation therapy in New Zealand is being conducted. This thesis reports the results of the first 12 patients available for analysis at the CRCHS.

## 1.1 The structure of the skin and its response to radiation

The skin is a multi-layered structure composed of the epidermis and dermis (11–13). The dermis consists of a papillary layer and a reticular layer (see Figure 1.1). The papillary layer contains nerves, hair follicles glandular tissue and blood vessels (6,11). The stem cells in the basal layer of the epidermis replace cells by dividing with daughter cells travelling to the surface, which takes approximately 2 weeks (11,13). The basal layer is continually dividing and thus is particularly sensitive to damage by ionizing radiation (6). Radiation therapy causes ionizing events and the production of free radicals which damage cellular DNA and can cause cell death (14). Stem cell division is impaired and thus normal tissue turnover is reduced. The continued assault on the basal layer from fractionated radiation therapy causes the stem cells to produce cytokines which recruit circulating immune cells, contributing to an inflammatory environment (15). This leads to chronic free radical production reducing the stem cell population further, resulting in radiation-induced skin reactions (15).

Acute skin reactions develop within 2 to 3 weeks of irradiation and exhibit varying degrees of severity, including erythema and dry and/or moist desquamation followed by a process of healing (16). Complete healing of the epidermis can take as long as 6 weeks as long as permanent damage has not occurred (17).

### Erythema

Erythema is defined as reddening of the skin and is caused by the dilation of capillary vessels within the dermis and oedema (17–19). The inflammatory reactions that cause erythema are mediated by cytokines. A histamine-like substance is released, leaving the skin red and itchy (18). Erythema can manifest by varying shades of red depending on the dose delivered to that area (18,19). Standard fractionation regimen (2Gy per fraction, 5 days a week) can show light erythema at total doses of 20–25Gy (17,19,20).

### Dry Desquamation

As the dose of radiation is increased, dry desquamation can develop. This is characterised by dry flaky skin (6,19). This occurs when new cells divide and migrate to the skin surface faster than the old ones are shed (18). This occurs approximately 4 weeks after the start of irradiation, following a 2Gy per fraction regimen (18,19).

Moist desquamation

Moist desquamation is manifested by blistering, peeling and sloughing of the skin's surface and often pain (6,21). It is caused by the complete destruction of stem cells in the basal layer and thus skin cannot be replaced at the surface (6,13). This usually occurs after 4 or 5 weeks of radiation, with doses of 40Gy or more, following a 2Gy per fraction regimen (21,22). Moist desquamation is the most clinically significant manifestation of all radiation-induced skin reactions.

## 1.2 Factors effecting the severity of skin reactions

The severity of radiation skin reactions is dependent on a number of intrinsic and extrinsic factors of which dose is a core influence (6,13,16,17,23). The intrinsic or patient-related factors include age, skin type, smoking, nutritional status, performance status, co-morbidities. The extrinsic factors include radiation dose, use of build-up material, and fractionation (16). Porock describes the factors affecting skin reactions as a conceptual framework and allocates each factor into a treatment, genetic or patient construct (16,23). These factors are listed in Table 1.1.

**Table 1.1 - Factors affecting skin reaction severity (adapted from (16,23)).**

Treatment	Patient	Lifestyle
Radiation dose	gender	obesity
Radiation volume	ethnicity	smoking
Radiation fractionation	age	nutritional status
Tumour site		comorbidities
Radiation technique		
Concurrent chemotherapy		

### 1.2.1 Treatment-related factors

#### **Dose, site and fractionation**

There is a close relationship between dose and fractionation regimen in the development of skin reactions, as these are based on tissue tolerances (16). Porock and colleagues reported a definitive dose-response relationship between severity of skin reaction and the dose received (23). At about 50Gy repopulation no longer mitigates the cells lost by radiation damage (17). Head and neck cancer patients often receive doses in excess of 60Gy to the tumour (24,25). Severe radiation dermatitis therefore cannot be avoided in these patients as the target volume is very close to the skin (7). Patients with tumours located close to the skin, as can be seen in breast and head and neck cancer patients, will receive a much higher dose to the skin than patients with deeper tumours in other body locations.

#### **Radiation type**

The effect of radiation on the skin is also dependent on the type of radiation used. Radiation particles have varying velocities, energies and ionisation potentials (17). Higher energy radiation, such as that

produced by linear accelerators, delivers maximum dose deep into the tissues, sparing superficial structures such as the skin from the highest doses(6,17).

### **Treatment planning techniques**

Recent advances in treatment planning have decreased skin dose and thus skin reaction severity. Intensity Modulated Radiation Therapy (IMRT) is an inverse planning technique that uses a sophisticated planning algorithm and non-uniform beam intensities to more accurately shape the dose of radiation to the target and help spare normal tissue compared to conventional 3 dimensional conformal radiotherapy (3DCRT) (26,27). The use of more complex planning techniques such as IMRT and Volumetric Arc Therapy (VMAT) have led to a reduction in moist desquamation for head and neck cancer patients (24,27). However grade 3 or higher dermatitis is still present in approximately 10% of patients and brisk erythema still occurs in the majority of patients (24,27). Areas of skin can be deliberately targeted to reduce the dose in that area, however some superficial areas within the target volume can still be at high risk (28).

### **Immobilisation and build-up (bolus) material**

Radiation therapy for head and neck cancer patients requires precise setup procedures due to the close proximity of organs at risk, such as the parotid glands and spinal cord to the tumour (29). Immobilisation devices are therefore important to reduce setup variation to ensure that the treatment is delivered to exactly the same volume every fraction (29). Interestingly, this dose build-up effect is also seen in skin folds, with the most severe radiation reactions in patients receiving high doses in areas of skin folds (23). Skin folds can trap moisture and thus lead to worse skin reactions and infection (28).

Radiation reactions are exacerbated by multiple tangential-to-skin beams and the use of immobilisation devices (7). Lee et al. conducted dosimetric studies evaluating the skin dose using extended field IMRT. The measurements on their phantom showed an increased dose to the skin when a thermoplastic mask was used, showing it had a build-up or bolus effect (30). Bolus is a tissue-equivalent material, acting as tissue, to allow the beam to deposit a higher energy closer to the surface. This causes the skin to absorb the higher dose that underlying tissue would have received which increases the skin reaction severity (16).

## Chemotherapy

Chemotherapy agents are used to destroy cancer cells on their own or improve the effects of radiation therapy by acting as a radiosensitiser (16,23). In head and neck cancer patients, Cetuximab increases the rate of severe skin reactions 10 fold compared to radiation alone, with the incidence of moist desquamation as high as 49% (31–33). Other chemotherapy agents that are likely to have an additive damaging effect to radiation on the skin are 5-Fluorouracil, Adriamycin (Doxorubicin), and Methotrexate (16). DNA has been identified as the critical target for platin-based agents such as Cisplatin, as well as inducing reactive oxygen species that can trigger cell death by different pathways (34). Palazzi et al. reported that adding chemotherapy to radiation for head and neck cancer patients (n=149) was the most important independent factor predicting worse toxicity on multivariate analysis (35).

### 1.2.2. Patient-related factors

#### Gender

Several gender-linked differences have been described for human skin. The stratum corneum and epidermis are thicker in men than in women (36). Men are more prone to skin cancer and bacterial and viral infections, whereas women are more prone to autoimmune and inflammatory diseases (37). This may explain the greater acute and long term radiation toxicities found in female head and neck patients in a study by Meyer et al. (38). The authors found Odds Ratios for developing acute (1.72) and late (3.96) toxicities for females (n= 110) compared to males (n=417). In a different study by Dehing-Oberrieje and colleagues, female lung cancer patients (n= 142) were also shown to have a higher rate of radiation-induced dysphagia (OR 1.65, p=0.011) than male patients (n=327) (39).

#### Ethnicity

It has been hypothesised that people with darker skin would experience less severe radiation-induced skin reactions than people with a fair skin (16). The increased number of melanocytes which protect the underlying stem cells from damage from Ultra Violet (UV) radiation is thought to also protect the cells from ionising radiation. One study found that patients with fairer skin had worse skin reactions but reacted better to a steroid cream than patients with a darker skin (40). This however was not supported by Ryan and colleagues who found that patients with darker skin actually reported worse skin reactions (41). Previous studies using Mepilex lite and Mepitel Film for breast patients failed to

show a correlation between skin type and radiation skin reactions (10,42). In fact some authors suggest that people with dark skin may in fact have worse skin reactions. Melanin does not protect the nucleus from ionising radiation but causes an increase in free radical production during melanin production, resulting in more rather than less DNA damage and worse skin reactions (15).

### **Age**

As a person ages, the epidermal turnover decreases resulting in thinner skin with a decreased healing capacity (23,43). Every stage of the healing process has shown age related changes in clinical studies (43). However, the effect of age on radiation-induced skin reactions is less clear. Turesson et al. failed to prove that age was significantly associated with acute skin reaction severity in a multivariate analysis for 402 breast cancer patients (44). Severe acute and late toxicities in clinical trial of 540 head and neck cancer patients were also not associated with age (38). In fact, younger age was shown by Palazzi et al. (35) to be a statistically significant predictor of radiation dermatitis ( $p=0.03$ ), in a study of 149 head and neck cancer patients.

## **1.2.3 Lifestyle-related factors**

### **Obesity**

Adipose tissue effects healing due to its hypo-vascularity and its release of specific adipokines that may inhibit the immune response (16,43). Obesity can also cause excessive wear on the skin through increased friction caused by skin on skin contact and larger skin folds (16,43). These skin folds can also harbour potentially harmful microorganisms which can cause wound complications (43). Meyer et al. reported in their study of 540 head and neck cancer patients that patients with a Body Mass Index (BMI) of greater than 25 were 1.88 times more likely to have severe acute or late radiation-induced toxicities than patients within the healthy weight range (38). Sharp et al. also found high BMI to be a significant factor predicting severe radiation skin reactions in a randomised study testing two different skin care formulations in 390 patients with breast cancer (45).

### **Smoking**

Smoking has been shown to not only increase the risk of several chronic diseases but also has a detrimental effect on wound healing (43). The supply of oxygen to tissues is compromised by vasoconstrictive effects of nicotine, as well as carbon monoxide aggressively binding to haemoglobin



in the blood, causing hypoxia (43). Sharp et al. reported that in addition to obesity, smoking was also significantly associated with severe radiation skin reactions on multivariate analysis (45).

### **Nutritional Status**

Nutrition plays a key role in wound repair. Glucose, in the form of carbohydrates, is the main energy source for cellular renewal and the formation of blood vessels (43). Protein deficiency decreases all metabolic activities, including the production and activity of immune cells thus increasing the susceptibility to infection. Proteins are responsible for a number of important processes including collagen synthesis and wound remodelling (43). Vitamins and several micronutrients have also been shown to be essential in the wound healing process especially Vitamin A, C, E, magnesium, copper zinc and iron (43).

### **Comorbidities**

There are a number of inherited syndromes that cause hypersensitive skin reactions in response to radiation. These include ataxia telangiectasia, Bloom's syndrome, Fanconi's anaemia, retinoblastoma, Down's syndrome and basal cell nevus syndrome (16,23). The genetic susceptibility of these diseases to radiation damage is thought to be linked to chromosomal fragility or failed DNA strand break recognition and mis-repair (46). Diabetes is a well-known factor influencing cellular repair. This is thought to be due to impaired vascularity which results in lack of nutritional support and poorly oxygenated tissues (43). Both oxygen and nutrients are essential in cellular repair and metabolism and promote healing.

### **Other factors that affect skin reaction severity in addition to those covered by Porock(16,23):**

#### **Stress**

Recent evidence suggests that patient stress can negatively affect wound healing. Any form of stress increases the production of glucocorticosteroids such as cortisol by the adrenal cortex. This produces a more inflammatory environment, fuelling the inflammatory skin reaction process (43,47). With respect to wound healing, high cortisol levels impair all three phases of wound healing, inflammation, proliferation and remodelling (48). Anxiety and depression as well as physical stress have been associated with delayed healing of chronic wounds in several clinical studies.

Ebrecht et al. (49) investigated stress and wound healing by assessing punch biopsy healing in 24 healthy males. The speed of wound healing was significantly negatively associated with Perceived

Stress Scores and elevated cortisol levels in the morning. Another study investigated the effect of laughter therapy on skin reaction severity in 37 breast cancer patients (50). This was not a randomised study but showed that the laughter therapy intervention group developed less severe skin reactions. In the laughter therapy group, grade 3 and 2 reactions were seen in 33% and 33% of patients respectively, whereas in the control group grade 3 and 2 reactions were seen in 36.8% and 47.4% of patients ( $p=0.053$ ). Although there has not been any research on stress and radiation-induced skin reactions, the fact that stress exacerbates inflammatory skin conditions such as atopic dermatitis and psoriasis (48) makes it plausible that stress may also aggravate radiation dermatitis.

### **Human Papilloma Virus (HPV)**

HPV infection has been associated with the development of head and neck cancer (51). P16 overexpression has been accepted as a biomarker for HPV oncoproteins (52). Becker-Schiebe et al. retrospectively assessed 79 head and neck cancer patients and found that p16 positivity was significantly associated with acute grade 3 skin toxicity. The authors stated that this finding may be explained by HPV infected mucosal tissue possibly enhancing radiation related inflammation by affecting the basal layer of the skin (52). Patients with HPV positive cancers have a better prognosis, which has been attributed to better local control due to the greater radiosensitivity of HPV positive tumours compared with HPV negative tumours (53).

### **Haemoglobin levels**

Up to 30% of cancer patients can present with anaemia largely caused by a blunted erythropoietin response, disordered iron metabolism, increased levels of inflammatory cytokines and tumour burden metabolic changes (54). Hypoxia has been shown to increase the genetic instability of cancer cells, which can result in daughter cells with diminished apoptotic potential and/or increased therapy resistance (55). Oxygen is known to increase the effectiveness of radiation therapy two-three fold. Oxygen forms oxygen-derived free radicals which increase radiation-induced DNA damage (56). The damage caused by other free radicals to the DNA backbone can be fixed under hypoxic conditions but made permanent by interactions with oxygen (56). The impact of haemoglobin levels on acute normal tissue toxicity during chemoradiation for cervical cancer was evidenced by high haemoglobin levels ( $>12\text{gm/dl}$ ) significantly worsening acute mucotaneous toxicity (57). A similar study for head and neck patients ( $n=79$ ) also found that the risk of severe skin toxicities was reduced for patients with hypoxic blood values before the start of their chemoradiotherapy treatment (52).

**Friction of radiation damaged skin**

The most recent addition to the “factors that affect skin reaction severity” has been described by Herst (15). In addition to being damaged on a daily basis by ionising radiation, skin is also subject to friction stresses caused by clothing and other body parts. This is particularly important for tumours close to the skin that already receive a much higher dose than deeper tumours. Breast and head and neck cancer patients are most likely to suffer from radiation-induced skin reactions due to the combination of high skin dose and high friction levels. This new angle of skin reaction severity has opened the road to new treatment approaches, which will be discussed in more detail later in this thesis and which forms the theoretical basis of the current thesis.

### 1.3 Prevention of radiation-induced skin reactions

Radiation-induced skin reactions are a common occurrence for breast cancer and head and neck cancer patients (16). However, the latest skin review by Chan et al. in 2014 (8) found no evidence to support the use of any topical agents for preventing radiation-induced skin reactions. Their review included 47 studies and analysed the effect of various interventions on development and symptom severity of skin reactions as well as several secondary objectives including quality of life. Oral therapies, skin care practices, topical ointments and some dressings were all included in the analysis. The authors commented on the small size of most studies and the lack of good quality randomised controlled trials. They did not discourage the use of soap for washing and deodorant. Practice across Australia and New Zealand is also inconsistent and a recent survey showed that 50% of respondent departments based their skin care advice on anecdotal evidence (9). Similar findings have been reported in Europe and the USA (58).

The following section provides an overview of the literature investigating topical agents for the prevention of radiation-induced skin reactions published since the review by Chan et al. It is not intended as a comprehensive systematic review and only includes English language articles available from the University of Otago. A total of nine studies were identified and are summarised in detail in Appendix A.

Two studies assessed the use of transparent dressings on skin reaction severity. Ariumra et al. (59) compared Airwall tape to conventional treatment of Dimethyl isopropylazulene for grade 1 reactions, Betamethasone valerate for grade 2 and Betamethasone valerate or Gentamicin sulfate for grade 3 reactions in 271 prostate cancer patients. Airwall tape was described as a colourless transparent tape, 7µm thick. The results did show a statistically significant difference between the development of grade 2 and 3 reactions between the intervention and control groups (21 and 0 vs 57 and 4,  $p < 0.001$ ). A total of 18 patients in the intervention group however stopped applying the film citing itching sensation, skin redness and folliculitis. This study was limited by the fact that it was not randomised and patients chose which group they wanted to participate in, creating unavoidable selection bias. The skin was assessed every two days until the patients finished and then the patients sent in photos of the skin for analysis once a week for a month. There was no mention of ensuring the photos were of sufficient quality for analysis. The authors said in correspondence dated 18<sup>th</sup> January 2016 that doses were compared using Dose Volume Histograms in the planning system but no independent skin dose measures were taken.

Herst et al. (10) compared the effect on skin reactions of a silicone-based film to aqueous control cream in a randomised intra-patient controlled RCT of 78 breast cancer patients. Participants had their breast/chest wall divided into two equal halves (medial and lateral) which were randomly assigned to either aqueous cream or Mepitel Film. Mepitel Film was applied prophylactically from the first day of radiation therapy. The assessors used the RTOG scale (60) and modified Radiation-induced Skin Assessment Scale (RISRAS) (19,61) to assess skin reaction severity three times a week during treatment and once a week for 4 weeks after completion of treatment. The results showed the skin underneath the Mepitel Film did not develop moist desquamation compared to 26% of aqueous cream treated skin. Overall, skin reaction severity was reduced by 92% ( $p < 0.0001$ ). This randomised study was much more robust than that of Arimura et al. as Herst et al. used patients as their own controls and TLDs to measure the dose to each skin area.

Recent evidence suggests that aqueous cream damages the skin barrier most likely due to the sodium lauryl sulphate (SLS) in its formulation (62,63). It is therefore no longer recommended as a leave-on emollient. Herst et al. also showed a higher rate of moist desquamation in the conventionally fractionated group (50Gy in 25 fractions) compared to the hypofractionated group (40Gy in 15 fractions) (10). This is important as hypofractionation is becoming increasingly common in this cohort of patients and is already the standard of care in the UK (64).

Three trials assessed the use of oils in preventing skin reactions. Rollman et al. (65) randomly compared emu oil to cotton seed oil in 45 breast and chest wall patients. They used a variety of skin toxicity assessment tools but did not find a statistically significant difference between both arms. Cottonseed oil was used as a control as it has the same appearance as emu oil and thus this was a double-blinded study. Cottonseed oil however is not considered standard of care in countries across Europe or the USA (58) and thus is difficult to compare the results of this study to other international studies. This study would have benefited from the measuring the actual skin dose in the intervention and control areas, as well as larger patient numbers.

On the other hand Cui et al. (66) compared olive oil to water in the prevention of radiation-induced skin reactions in 94 nasopharynx patients. They used the RTOG scoring and the Visual Analogue Scale (VAS) to assess skin reaction severity. The incidence of more severe reactions was less in the intervention group (6.4% vs 27.7%  $p < 0.01$ ) as were the average VAS scores. The results were attributed to the antioxidant and anti-inflammatory effects of the olive oil. This study would have

benefitted from independent assessment of the dose to the skin similar to the study above. It also did not mention what type of planning technique was used for these patients as IMRT can significantly reduce skin toxicity (24,27). Water was probably not the most appropriate control to use, as many centres recommend the use of a simple emollient cream (9).

Palatty et al. (22) compared a turmeric and sandalwood oil containing cream versus baby oil in 50 head and neck cancer patients. There was a significant difference in the incidence and severity of grade III skin reactions in the cream group compared to baby oil. Similar to most studies, this study also lacked an independent dose verification to the skin. The investigator was blinded but the patients were not. The investigator chose the area of worst skin reaction in the whole treatment area which would have varied between patients introducing selection bias. The criteria for choosing which area had the worst skin reaction were not reported.

Three studies evaluated the use of creams in preventing radiation-induced skin reactions. Chan et al. (67) compared Allantoin to aqueous cream in 174 breast, lung and head and neck patients. Although Allantoin was supported by anecdotal evidence, it did no better than aqueous cream in preventing skin reactions. The trial was strengthened by its double-blinded design, however similar to other studies there was no independent measure of skin dose and the inclusion of several different types of cancer made the results harder to compare. The use of aqueous cream has been largely discredited and should not be used as a leave on emollient(62,63,68).

Hindley et al. (69) compared the glucocorticosteroid Mometasone furoate (MF) to Disporboase (D) cream, which is an emollient similar to aqueous cream but does not contain SLS. A total of 120 breast cancer patients participated in the trial. The trial used the modified RTOG (60) scoring as well as diastron reflectance spectrometer to measure erythema and Hospital Anxiety and Depression (HAD) Scale(70) and the Dermatology Life Quality Index (DLQI)(71) questionnaires. The results showed a statistically significant difference in mean RTOG scores favouring the glucocorticosteroid, (mean difference 0.123  $p=0.46$ ). Patients in the MF group showed DLQI scores that were significantly less than the D group, but only for week 4 and 5. This study is unique in that it used a reflectance spectrometer in order to reduce observer bias when assessing degree of erythema in the skin, and its use of quality of life scores for the patients.

The studies by Chan et al. and Hindley et al. have however been criticised, as the difference in RTOG scores for Hindley et al. was small (mean score difference of 0.123) and may not have clinically

significant despite being statistically significant (72). However, this may just reflect the insensitivity of the RTOG scale. Using a more sensitive scale such as the RISRAS (19,61) may have produced a more pronounced difference. The trial by Chan et al. was praised for at least testing a natural based product to try to back up anecdotal evidence (72).

Togni et al. (73) compared a Boswellia-based cream known for its strong anti-inflammatory properties to a 'base cream' on 114 breast cancer patients. Assessments used were RTOG scale and digital evaluation of colour magenta saturation using adobe photoshop. In patients using Boswellia cream the mean value of skin damage using photoshop was lower than that of the base cream group (10.1% vs 13.3%),  $p=0.009$ ) however the difference in RTOG scores did not reach significance. This trial was not blinded and some patients reported disliking the smell of the Boswellia cream, and a non-absorbed residue was noted on patients' skin. The trial also mentioned trends in itching and burning sensation however the assessment used to measure this was not mentioned. The assessments were done up to the last day of treatment and no follow-up was done after this. This is important as the peak skin reaction has been reported to occur two weeks after the completion of radiation therapy (42,74), so the peak skin reaction would not have been recorded.

Finally, Manas et al. compared a water based gel plus Lactokine fluid (R1+R2) to a Urea cream (75). The study included 98 head and neck and breast cancer patients. The patients were assessed at four clinic visits, the week before treatment, 3-4 weeks from the start of treatment, at the end of treatment and then two weeks after treatment finished. CTC toxicity criteria were used as well as European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaires. Fewer patients had skin reactions in the intervention group at all follow up appointments, and the results were statistically significant. At the fourth follow-up visit, 33% of patients presented with an acute skin reaction in the intervention group compared to 66% of patients in the control group ( $p=0.003$ ). The authors however failed to give any information on patient demographics. It was difficult to know how good patient compliance was as they were only seen four times during the trial period. There was also no dosimetric evaluation of skin dose and the use of two very different cancer sites made the results difficult to interpret, as no sub-group analysis was described. The authors also said that quality of life was improved for the intervention group, but no results or statistics were included in the publication.

## 1.4 Management of Acute radiation-induced skin reactions

The 2014 review by Chan et al. also did not find any significant studies of sufficient quality that showed any product was superior in managing radiation skin reactions once they had occurred. A literature review by Russi et al. in 2015 with a panel consisting of 32 multidisciplinary experts sought to establish consensus guidelines for the management of acute skin toxicity for head and neck cancer patients (7). One of the main limiting factors mentioned in this study was that many studies are small or retrospective and there are not many that specifically include head and neck cancer patients. They concluded that there was insufficient evidence to support using any particular dressing or advanced medication for the management of skin reactions, and that protecting the skin for further trauma was important. This section provides an overview of the literature investigating topical agents for the management of radiation-induced skin reactions published since the Russi et al. review, and includes trials using dressings that protect the skin from trauma, including Mepilex Lite (42). Mepitel Film was mentioned by the authors but the irregularity of the skin surface in head and neck cancer patients was mentioned as a difficulty in applying the Mepitel Film in this area. (7). Management is considered any strategy aimed at controlling established reactions in the form of erythema or dry/moist desquamation (8). It is not intended as a comprehensive systematic review and only includes English language articles available from the University of Otago. Studies that were single arm or pilot studies were excluded. A total of three studies were identified and summarised in Appendix B.

Mepilex Lite dressings were examined by the same group that assessed Mepitel Film for the prevention of radiation-induced skin reactions. Paterson et al. (42) compared Mepilex Lite to aqueous cream in 80 chest wall patients once erythema had occurred. Both products have a soft silicon contact layer which adheres to healthy skin but does not stick to open wounds and minimises trauma on the skin from dressing changes. Bonded to the silicone webbing is a foam layer (Mepilex Lite) or a breathable film (Mepitel Film). This trial was robust in its intra-patient controlled randomised design, the use of the RISRAS measure which is sensitive and has a patient component. Although there were no statistically significant difference in the incidence of moist desquamation between dressing and cream, the dressing reduced the overall severity of the skin reactions by 40%, which was statistically significant ( $p < 0.001$ ). In this multicentre trial dose to the skin was measured in two departments and inferred from treatment plans in two other departments. The authors mentioned that the dressings did not stick well on all areas and that because of the lack of transparency and bolus effect, they needed to be removed during radiation therapy.



Zhong et al. (76) assessed Mepilex Lite in 88 nasopharynx patients for management after moist desquamation. Similar to Patterson et al. they used RISRAS as well as the VAS pain and a Likert scale for neck mobility, sleep and appearance disturbance. The study showed there was a significant difference in time to wound healing with Mepilex Lite compared to the control in favour of Mepilex Lite (Median 16 days compared to 23 days,  $p=0.009$ ). This study was difficult to assess however as the authors described time to wound healing as the complete re-epithelisation of all wounds, but then said the endpoint was dry desquamation. The planning techniques of patients varied considerably with 2D, 3D and IMRT utilised, and skin dose was not assessed.

Bazire et al.(77) found that Hydrosorb dressings were no better than a simple water based spray in managing skin reactions in 278 breast cancer patients. Colourimetric evaluation was used with a chromameter for erythema. VAS was used to assess pain and DLQI was used to measure quality of life. Patients put the hydrosorb on themselves at home, with no mention of reproducibility of placement. Skin dose was also not assessed.

## 1.5 Aim and Objectives

### Aim

The overall aim of this randomised controlled feasibility study was to investigate whether Mepitel Film dressings were superior to Sorbolene cream in reducing or managing radiation-induced skin reactions in patients with head and neck cancer.. In order to avoid skin thinning by aqueous cream, Sorbolene cream was used as a control cream. The effect of Mepitel Film was to be tested in a prophylactic (applied from day one of radiation therapy) and a management setting (applied when erythema is visible).

### Hypotheses

1. Mepitel Film is superior to Sorbolene cream in decreasing the severity of acute radiation-induced skin reaction in patients receiving radiation therapy for head and neck cancer
2. The prophylactic protocol is superior to the management protocol in protecting the skin from friction and reduce skin reaction severity

In order to test these hypotheses this research consists of a randomised, controlled, multi-centre, international, open label intra-patient feasibility study. Patients are being recruited from public hospitals in Dunedin and Christchurch in NZ and Drum Tower Hospital in Nanjing in China. This thesis analyses a subset of 12 patients (six on the management protocol and six on the prophylactic protocol) recruited at the Canterbury Regional Cancer and Haematology Service (CRCHS) at Christchurch Public Hospital.

### Objectives

1. To determine whether or not Mepitel Film is superior to standard Sorbolene cream in reducing skin reaction severity when used in a management setting.
2. To determine whether or not Mepitel Film is superior to standard Sorbolene cream in reducing skin reaction severity when used in a prophylactic setting.
3. To determine whether perceived stress levels affect skin reaction severity

**Measures**

1. Skin reaction severity was measured three times a week during radiation treatments and once a week for 4 weeks after completion of treatment using modified RISRAS(19,61) and modified RTOG(78).
2. Stress levels were measured using the New Zealand validated Distress screening tool(79) once a week.
3. Dose to the skin was measured using thermoluminescent dosimeters (TLDs)

## Chapter 2 Methods

### 2.1 Research Design

The overall feasibility study is a multi-centre international randomised intra-patient controlled pilot study comparing the efficacy of Mepitel Film versus Sorbolene cream in decreasing acute skin reactions during radiation to the head and neck. This thesis analyses the results of the first 12 patients of this trial, recruited at CRCHS. The first six patients were on a management protocol, where the interventions were applied from the moment faint erythema was visible. The last six patients were on the prophylactic protocol where the interventions were used from day one of radiation therapy. The trial is continuing to recruit patients in NZ and China at the time of writing.

In order to make the results of this trial comparable to the results of previous trials involving Mepitel Film (10) and Mepilex Lite (42), a similar methodology was adopted. This included the use of similar skin reaction severity scoring instruments, the number of times skin reaction severity was determined and the intra-patient design, described in more detail below.

The trial was approved by the University of Otago Ethics Committee for Health Research in September 2014 (Reference number H14/111). Locality ethics approval was also obtained with the CDHB research office on 23<sup>rd</sup> December 2014. The trial is registered with the Australia and New Zealand Clinical Trials Registry (ACTRN12614000932662). The protocol was changed from a management to a prophylactic protocol in order to assess the effect of Mepitel Film on skin reactions when applied on the first day of treatment instead of at presentation of erythema. The amendment was approved by the Ethics committee on 17<sup>th</sup> September 2015. The statistical significance between differences in Mepitel Film and control RISRAS scores was determined by paired two-tailed student T-test using Excel (Microsoft v 2010; Redmond Campus, Redmond, Washington, USA).

### 2.2 Funding

Salary for the Academic Principal Investigator/trial coordinator, Associate Professor Patries Herst was paid for by the University of Otago Wellington. Salaries of the research radiation therapist, Bachelor of Radiation Therapy (Honours) student and author of the thesis, Hayley Wooding, and Clinical lead/Clinical Principal Investigator (Dr Iain Ward) were paid for by the CDHB. The course fees for the

Bachelor of Radiation Therapy (Honours) were funded by the Christchurch Hospital Oncology Trust fund.

Mepitel Film was provided free of charge by Mölnycke Healthcare AB. Travel vouchers for patients (\$100 each) and Sorbolene cream (\$25 each) were paid for by a research grant of the University of Otago. Travel vouchers were given to all patients participating in the trial to account for the increased number of follow-up appointments they were asked to attend as part of the trial compared to non-trial patients.

## 2.3 Participants

### 2.3.1 Eligibility

Inclusion criteria:

- Age over 18
- Receiving radiation therapy for mucosal squamous cell carcinoma (SCC) for head and neck cancer
- Able to attend 4 follow-up sessions.
- Consent to removing facial hair at the treatment site

Exclusion criteria:

- Metastatic disease
- Previous radiation therapy to the head and neck area
- Any skin conditions that can aggravate radiation-induced skin reactions
- Karnofsky score < 70
- Patients living outside of Christchurch

Participants were excluded if their Karnofsky score (80) was less than 70. This was because patients were required to apply the Sorbolene cream easily themselves. They also were required to fill in the patient component of the RISRAS scoring and come in each day for treatment, which would have been a struggle for patients with a score less than 70.

### 2.3.2 Participant numbers

The pilot in Christchurch aimed to recruit 20 patients over a 2 year period. As this is a pilot study to test the feasibility of using Mepitel Film in this cohort of patients, the total number enrolled was not

established by a power calculation, but depended on the number of patients who presented to the hospitals over the trial period. This thesis will only report on the analysis of the first 12 patients on the trial; six of whom were on the management protocol and six who were on the prophylactic protocol.

### **2.3.3 Consent**

Patients were given verbal as well as written information about the trial in the form of a participant information sheet (Appendix C). This was done either at their CT scan (prophylactic protocol) –or day 1 of treatment (management protocol) by the researcher. The patients were given the opportunity to discuss the trial information with whanau and were given the contact number of the researcher if they had any questions. Written informed consent was signed by the patients on the day of the first radiation treatment (prophylactic protocol) or a few days after their first day of treatment (management protocol) (Appendix D). Patients also consented to the use of photos for the trial, as long as they could not be identified from them, which was specifically mentioned on the written consent form.

## 2.4 Treatment

### 2.4.1 Radiation Treatment

Treatment was given according to the department radiation therapy prescription guidelines. This is described in the following table (Table 2.1).

**Table 2.1. RT prescription guidelines for head and neck patients at Canterbury Regional Blood and Cancer Service.**

	3DCRT	IMRT
<b>Definitive RT</b>		
High-dose volume	70Gy/35#	66Gy/30#
Intermediate-dose volume	60Gy/30#	60Gy/30#
Elective volume	50Gy/25#	54Gy/30#
<b>Postoperative RT</b>		
High-dose volume (residual disease; positive margins)	66Gy/33# - 70Gy/35#	66Gy/30#
Intermediate-dose volume (tumour bed)	60Gy/30#	60Gy/30#
Elective volume	50Gy/25# - 54Gy/27#	54Gy/30#

The planning technique, dose, the use of bolus and chemotherapy information was recorded for each patient (Table 3.1). All patients were treated in the supine position on a flat board that attached to the treatment couch. Each patient also had a thermoplastic mask made that reached down to their shoulders. Radiation therapy was delivered using either a 3DCRT technique or IMRT/VMAT with 6MV photons.

### 2.4.2 Chemotherapy

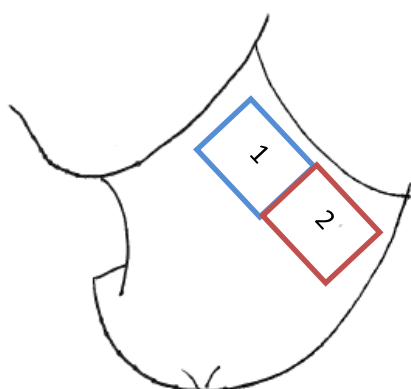
Patients who had stage III or IV disease also had chemotherapy at the same time as their radiation. This was with weekly IV cisplatin, 40mg/m<sup>2</sup>. Meta-analysis has shown a benefit of chemotherapy with these patients (3).

## 2.5 Intra-patient design, randomisation and blinding

This was an intra-patient comparison where patients acted as their own controls, in order to remove potentially confounding factors such as treatment- and patient-related differences in skin reaction severity between patients (described in section 1.2). Any differences in skin reaction severity between skin covered in Mepitel Film or Sorbolene Cream are not likely to be due to treatment- and patient-related factors in the cohort for this pilot study. This design also meant that all of the patients were able to experience what it is like to have Mepitel Film applied to their skin.

### 2.5.1 Randomisation

The control and intervention areas were divided into either inferior and superior halves or medial and lateral halves by the radiation therapy researcher. Mepitel Film was allocated randomly by pre-prepared computer generated randomisation charts created by a Biostatistician at the University of Otago, Wellington. Randomisation removes allocation bias, ensuring that Mepitel Film is not allocated predominantly to the site that is likely to develop the least severe skin reactions. Mepitel Film was allocated to either superior/left or inferior/right depending on how the researcher divided the areas (see Figure 2.1). Randomisation was conducted via a randomisation form (Appendix E) which was sent by fax to the principal investigator Dr Ptries Herst at the University of Otago, Wellington. The principal investigator had no direct involvement with the patients.



**Figure 2.1. Diagram of study area; (1) = control area and (2) = intervention area.**



### 2.5.2 Blinding

Blinding is important to reduce researcher and patient bias. This type of bias occurs when researchers and patients inadvertently score their preferred intervention more favourably than the other option. Unfortunately, the researcher and the patients in this pilot study were unable to be blinded. This is because the Mepitel Film stayed in place for many days and was very different in appearance than the Sorbolene Cream. This means that a certain amount of researcher and patient bias cannot be excluded.

## 2.6 Procedure

The intervention and control areas were drawn onto the patient with semi-permanent marker and were also transcribed onto a thin transparent mylar. The mylar included anatomical landmarks of the patient's face to ensure the control and intervention areas could be accurately reproduced in case the drawn on marks or the Mepitel Film came off.

### 2.6.1 Control area (Sorbolene)

Dermasoft® Sorbolene cream contains Deionised Water, Glycerin, Cetearyl Alcohol, Mineral Oil, Ceteth 20, Polysorbate 60, Paraffin, Benzyl Alcohol, Methyl Paraben and Propyl Paraben and can be used as a moisturiser on sensitive skin (<http://www.pharmacydirect.co.nz/Dermasoft-Sorbolene-Cream-375g.html>). Sorbolene does not contain sodium lauryl sulphate (SLS). All patients were asked to apply Sorbolene cream to the control area twice daily. Patients were advised to continue using the cream until moist desquamation occurred, at which point they were to cease using the cream and just use salt water bathing as per the department skin care guidelines (Appendix F).

### 2.6.2 Intervention area (Mepitel Film)

Mepitel Film consists of soft silicone webbing contact layer which adheres closely to the folds of the skin, complemented by a breathable transparent film. Mepitel Film was cut according to the mylar marks and applied to the area it was randomised to. Mepitel Film was applied to the patient's neck in the extended position as this made it easier for the patient to move their neck once the Mepitel Film was applied. Dressings were replaced as needed. Mepitel Film was left in place for as long as possible but was replaced if it had significant peeling on the edges of the Mepitel Film. Mepitel Film was applied during treatment and for 4 weeks afterwards, as per the trial protocol. If moist desquamation occurred Mepitel Film was removed and patients were told to use salt water bathing as per the department skin care guidelines.

Herst et al. (10) determined in a previous trial that Mepitel Film has a negligible bolus effect of 0.12mm and thus was left on during radiation treatment.

### 2.6.3 Timing of the intervention

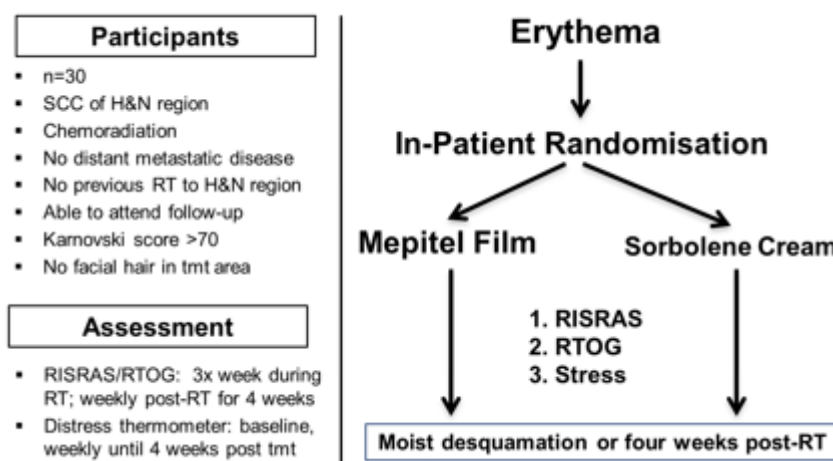
Previous skin trials conducted in breast cancer patients showed that Mepitel Film is most effective when used prophylactically, from day one of radiation therapy (10). However, radiation therapy for

head and neck cancer patients is more complicated and individualised depending on the location and stage of the tumour. The dose to the tumour (and the skin) is higher and cisplatin chemotherapy is administered concurrently in many of the patients. It was expected that it would be difficult to predict where the worst reactions would occur and waiting till erythema developed would circumvent that problem. Therefore, the first six patients were enrolled on the management protocol.

In addition, skin reactions are not necessarily the worst side effects of radiation therapy for these patients: oral mucositis is likely to have a more significant impact on patient quality of life (QoL). The team was expecting that patient compliance could be poor, because patients were likely to be very ill and because of the cohort demographics (older, often with substantial alcohol and tobacco usage). The researchers expected that compliance (and the motivation to use Mepitel Film) would be better if there was obvious erythema. Therefore the trial was started using the management protocol. After six patients, it became obvious that the results were disappointing and we changed over to the prophylactic protocol to try and decrease friction damage and thus improve the skin reaction reducing effects of the Mepitel Film.

## Management protocol

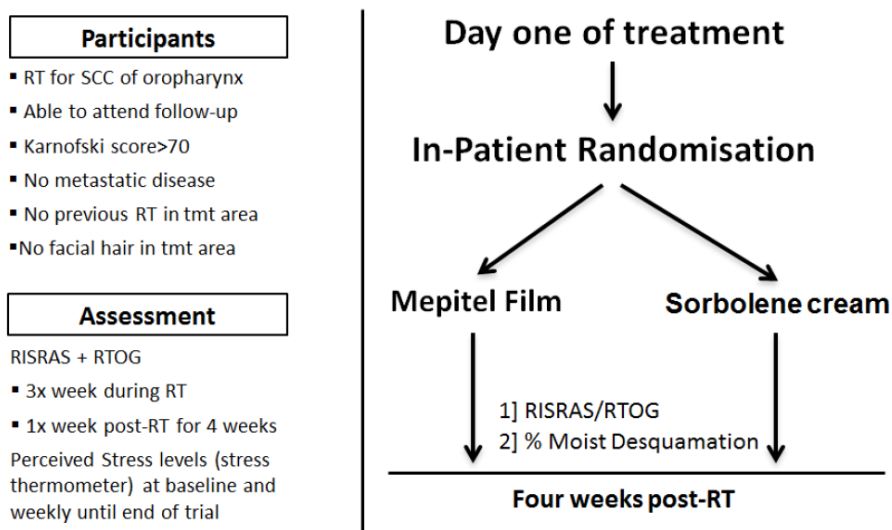
At the first sign of erythema, the area was divided into 2 equal halves. It was decided that the halves had to be on the neck rather than the face in order to improve the adhesion of the Mepitel Film to the skin and increase patient compliance. One half was randomised to Mepitel Film, the other half was the control area randomised to Sorbolene cream. The researcher checked each patient's skin daily for erythema. Erythema was also verified against the Radiation Oncologist's (RO) assessment in MOSAIQ, the patient management software system used at CRCHS.



**Figure 2.2. Management Trial Schema.**

## Prophylactic protocol

On the first day of treatment, an area on the neck was selected from the treatment plan that had a relatively even dose distribution and was likely to get a dose of at least 40Gy to the skin. This area was divided into 2 equal halves. One half was randomised to be covered with Mepitel Film, the other half was the control area to be treated with Sorbolene cream. The area had to be at least 10cm by 5cm in order to adequately divide it into 2 equal study areas. The area also needed to have a relatively homogenous dose in order for the Mepitel and Sorbolene areas to receive approximately the same dose. This limited the areas that could be chosen significantly due to the nature of IMRT/VMAT plans used for treatment planning. This method of choosing the research area was not as accurate as the management protocol as the patient was not usually in exactly the same position as in the scan. However, the dose to the skin covered in Mepitel Film and cream was measured using TLDs to independently verify skin dose and determine whether or not differences in skin dose could potentially have affected skin reaction severity.



**Figure 2.3. Prophylactic Trial Schema.**

## 2.7 Measurements

### 2.7.1 Skin reaction severity

The patient's skin was examined each day until erythema occurred. Once erythema had developed, skin reaction severity was measured using the modified RTOG (60) and modified RISRAS (61,81) in both the control and intervention areas. Scoring was done three times a week for the rest of the radiation treatment. After completion of treatment patients were seen once a week until 4 weeks after RT because skin reaction severity tends to peak after completion of treatment (42,74).

The RISRAS scoring scale was used because of its high sensitivity; small differences in skin reaction severity will be evident that may not be evident in the more commonly used and less sensitive RTOG grading system. RISRAS was developed by Noble-Adams (61) and later modified by MacBride (81). The researcher component of RISRAS scores the visible stages of reaction (erythema, dry desquamation, moist desquamation or necrosis) separately and gives further details on the percentage of the area of affected skin. The modified RTOG scale allows for the distinction between brisk erythema and patchy moist desquamation which is lost in the original RTOG or CTCAE scales (82,83). The modified RTOG only determines the severity of the skin reaction severity and not the extent of the area affected.

The RISRAS tool also includes a patient component, asking the patient to rate their level of discomfort, pain, itchiness, burning and the effect the skin reaction has on their day to day life, which allows for a more complete assessment of the patient experience.

The modified RTOG scale was used in addition to RISRAS to enable direct comparison of the results of this pilot study with those of previous studies.

Table 2.2. Skin reaction severity according to RISRAS and RTOG.

RISRAS (total scores between 0 and 36) <sup>a</sup>					
Researcher Component (total scores between 0 and 24)					
<b>Erythema (E)</b>	<b>0</b> Normal skin	<b>1</b> Dusky pink	<b>2</b> Dull red	<b>3</b> Brilliant red	<b>4</b> Deep red-purple
<b>Dry Desquamation (DD)</b>	<b>0</b> Normal skin	<b>1</b> (<25%) <sup>b</sup>	<b>2</b> (25%-50%)	<b>3</b> (50%-75%)	<b>4</b> (>75%)
<b>Moist Desquamation (MD)</b>	<b>0</b> Normal skin	<b>1.5</b> (<25%)	<b>3.0</b> (25%-50%)	<b>4.5</b> (50%-75%)	<b>6</b> (>75%)
<b>Necrosis (N)</b>	<b>0</b> Normal skin	<b>2.5</b> (<25%)	<b>5.0</b> (25%-50%)	<b>7.5</b> (50%-75%)	<b>10</b> (>75%)
Patient Component (total scores between 0 and 12)					
Symptoms	Not at all	A little	Quite a bit	Very much	
<i>Is your skin in the treatment area tender, uncomfortable or painful?</i>	<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>	
<i>Does your skin in the treatment area itch?</i>	<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>	
<i>Do you feel any burning sensation on your skin in the treatment area?</i>	<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>	
<i>Have your skin reactions and/or your symptoms affected your day to day activities?</i>	<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>	

Modified RTOG					
Grade 1	Grade 1.5	Grade 2	Grade 2.5	Grade 3	Grade 4
Follicular, faint or dull erythema	dry desquamation	Tender or bright erythema	patchy moist desquamation	Confluent moist desquamation other than skin folds	Ulceration; haemorrhage; necrosis

### 2.7.2 Skin dose

The research area was to receive a homogenous high dose (>35Gy). This was determined using planning software to extrapolate the dose to the skin, which only gives an approximation of dose and not an absolute dose. Because total dose is such an important factor in skin reaction severity and thus a potential confounder in this study, the actual dose to the Mepitel Film and Sorbolene treated skin was determined for each patients, using thermoluminescent dosimeters (TLDs). For each patient a set of 3 TLDs were placed in the centre of the control and intervention areas (see figure 2.4). The TLDs were provided and measured courtesy of the Southern DHB Oncology and Haematology Service. An average dose was taken from these TLDs to determine the dose delivered to the control and intervention areas of the skin. These were labelled as Mepitel Film or Aqueous cream TLDs, as that was what they used in a previous study(10). As stated previously, Sorbolene cream was the actual control cream used in this cohort.



**Figure 2.4 Photo of Mepitel and Sorbolene areas TLDs for patient CRT-01.**

### 2.7.3 Distress levels

There is some evidence that increased cortisol levels due to stress can delay wound healing (43,47,48). A distress screening tool for oncology patients was first developed by the National Comprehensive Cancer Network specific for oncology patients. An impact thermometer was developed and added to the tool by Akizuki et al. (79,84). The tool consists of two thermometers that the patient uses to rank their perceived distress levels in the last week (on a scale of 0-10) and what impact that has had on their life (from 0-10). This distress tool also features different types of stressors in 5 domains (spiritual, practical, family, emotional and physical). The patient then indicates by ticking a series of boxes within these domains to indicate which of these potential stressor have affected them in the past week (Appendix G).

#### **2.7.4 Exit questionnaires**

Patients were given an exit questionnaire asking about their experience of being on the trial and the advantages or disadvantages of the Mepitel Film on completion of their follow-up period of 4 weeks. 11 out of 12 patients completed the questionnaire (Appendix H).

#### **Endpoint**

Because Mepitel Film is permeable to gases but not to moisture, moist desquamation was the endpoint of this trial. Patients who developed moist desquamation were treated according to departmental guidelines.

#### **Withdrawal from the study due to adverse events**

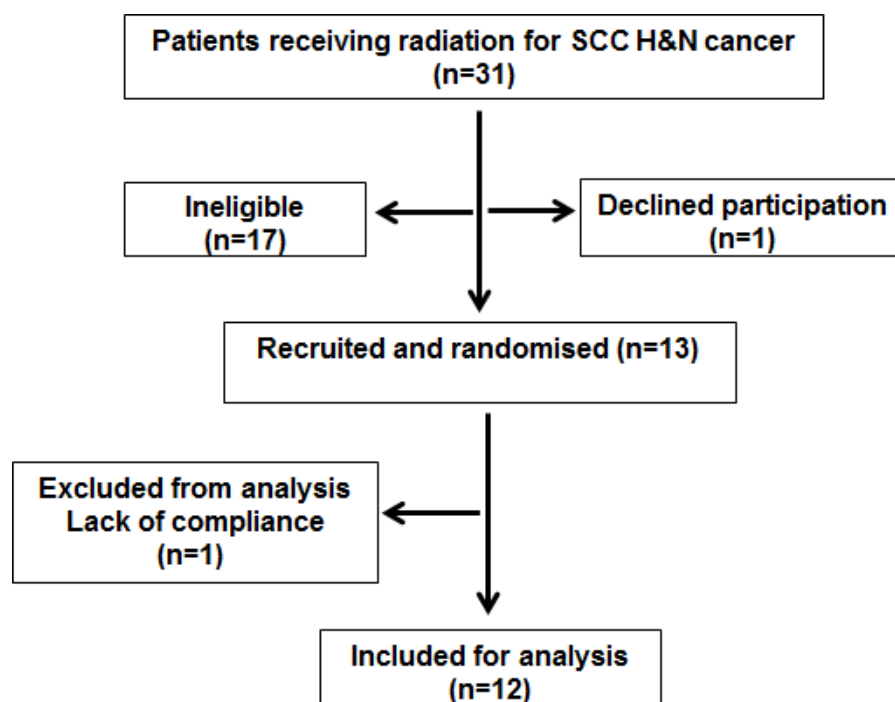
Mepitel Film and Sorbolene cream are both relatively hypoallergenic and do not contain any components known to have a harmful interaction with the skin. If a patient develops an intolerance to either product, substitution will be at the Oncologist's discretion. In the event of intolerance the patient would be withdrawn from the trial but the information gathered would still be part of the final analysis up until the time of withdrawal, unless the patient requests otherwise.



## Chapter 3 Results

### 3.1 Patient recruitment

This analysis includes patients recruited from December 2014 to December 2015 at the Canterbury Regional Blood and Cancer Service. The consort diagram below (Figure 3.1) summarises the accrual process. During this period 31 patients were screened for eligibility. Thirteen of these lived in another region and thus were excluded because they were unable to attend the follow-up appointments. Three patients were deemed unacceptable for inclusion by the oncologist. The first patient had poor health literacy and poor English. Another patient was extremely anxious and required medication. The third patient was unable to speak or read well making consent difficult. One patient was only having radiation to the face and this was not deemed appropriate for trial inclusion. One patient was not interested in participating. The remaining 13 patients were given written and oral information about the trial when they came for their CT scan. This allowed at least ten days for the patient to discuss trial involvement with their friends and family if they wished to. The researcher saw the patients again during the first two days of their treatment where the patients signed the consent form and were randomised. One of these patients kept applying Sorbolene cream in the Mepitel area, resulting in the Mepitel falling off, and thus was excluded from analysis due to non-compliance. The first 6 patients were enrolled in the management protocol, and the next 6 patients were enrolled in the prophylactic protocol.



**Figure 3.1. Consort Diagram: flow of patients through the trial.**

### **3.2. Patient demographics**

A total of 13 patients were recruited into the study between 27<sup>th</sup> December 2014 and 30<sup>th</sup> December 2015. Results from the 12 fully compliant patients were used in this analysis. The patient demographics are shown in Table 3.1. The cohort consisted of ten men and two women with an average age of 59 years (range 40-83 years). Most patients (n=10) identified as New Zealand European descent, with two patients identifying as Maori. Most patients (n=11) received 66Gy in 30 fractions using an inverse planning technique (IMRT and VMAT) because of the advanced disease stage (III or IV); whereas the only 3DCRT patient had stage I disease. With respect to HPV status; eight of the 12 participants' tumours tested positive, one tested negative, and the remaining three patients' tumours were not tested for HPV status. Baseline information was obtained from each patient with regard to smoking, alcohol use and diabetes status. A total of seven out of 12 patients had a history of smoking. The Fitzpatrick skin type scale (Appendix I, (85) )was used to assess skin type. The majority of patients had skin type III. None of the patients had diabetes. One patient had bolus with 3DCRT planning. Eight out of the twelve patients also had concurrent chemotherapy as part of their treatment. Patient numbering was done according to if they had chemotherapy and radiation therapy (CRT), or radiation therapy alone (RT)

Table 3.1 Patient Demographics

Patient ID	protocol	Primary	Stage	Sex	Dose	RT	HPV	Age	BMI	Ethnicity	Smoker	Sun	Skin type
CRT01	Management	Oropharynx	IVB	M	66	IMRT	+	52	28.2	Maori	ex	often	VI
CRT02	Management	Rt glottis	I	M	63	3DCRT	unknown	56	27.5	NZ Eur	ex	often	III
CRT03	Management	Tonsil	III	F	66	IMRT	+	40	19.2	NZ Eur	ex	rarely	III
CRT04	Prophylactic	Left retromolar trigone	III	F	60	IMRT	negative	55	22.5	NZ Eur	ex	often	III
CRT06	Prophylactic	Tonsil	IVA	M	66	VMAT	+	63	21.5	Maori	Y	rarely	IV
CRT07	Prophylactic	Tonsil	IVA	M	66	IMRT	+	56	26.9	NZ Eur	ex	often	IV
CRT08	Prophylactic	Tongue	IVA	M	66	VMAT	+	57	24.3	NZ Eur	N	often	III
CRT09	Prophylactic	Left tonsil	IVA	M	66	VMAT	+	58	22	NZ Eur	N	rarely	III
RT01	Management	Base of tongue	IVA	M	66	IMRT	+	52	29	NZ Eur	N	rarely	III
RT02	Management	Lower gum	IVA	M	60	IMRT	unknown	72	21.8	NZ Eur	ex	Often	IV
RT03	Management	Skin of lip (mets in neck nodes)	IV	M	60	IMRT	unknown	83	25.5	NZ Eur	N	rarely	III
RT04	Prophylactic	Unknown primary	III	F	66	VMAT	+	64	30	NZ Eur	N	often	III

### 3.3. Dose to the skin

Because the dose to the skin is the main factor in skin reaction severity and therefore a possible confounder in this trial, the dose to the skin underneath Mepitel Film and Sorbolene control cream was measured for each patient, using TLDs (see Table 3.2). Unfortunately, the same set of TLDs was used for both CRT04 and RT04 and thus the dose data from these two patients could not be used in this analysis. There was a 1Gy increased mean dose to the skin in the Mepitel Film area (50.95Gy) compared to the control area (49.43Gy). This was not statistically significant ( $p=0.137$ , student t-test). It is therefore unlikely that skin dose would have affected skin reaction severity or the incidence of moist desquamation.

**Table 3.2 TLD dose to Mepitel and control (Sorbolene) areas.**

	Dosimetry (Gy)	
Patient ID	Mepitel	Control
CRT01	57.17	53.83
CRT02	48.99	48.92
CRT03	50.76	50.28
CRT04		
CRT06	52.11	52.5
CRT07	51.03	47.94
CRT08	50.26	44.19
CRT09	46.14	49.48
RT01	48.43	49.26
RT02	49.19	43.82
RT03	55.38	54.12
RT04		
Ave	50.95	49.43
SD	3.28	3.54
SEM	1.09	1.18
p-value	0.137	

### 3.4 Skin reaction severity

#### 3.4.1. Average RISRAS scores

RISRAS scores were compared between the Mepitel Film and the Sorbolene control areas for both the management (Figure 3.2; Tables 3.3 and 3.4) and prophylactic (Figure 3.3; Tables 3.3 and 3.5) protocols. The researcher, patient and combined scores were analysed. A paired two-tailed T test was used to evaluate whether the differences were statistically significant. A p value of less than 0.05 was used as the threshold for statistical significance. Figure 3.2 visualises differences between both protocols.

**Table 3.3 Individual break down of RISRAS scores of all patients.\***

	Average RISRAS scores					
	Mepitel Film			Sorbolene		
	Combined	Researcher	Patient	Combined	Researcher	Patient
CRT01	3.78	2.33	1.44	4.5	2.56	1.94
CRT02	1.4	1.1	0.3	3.45	2.15	1.3
CRT03	4.92	2.85	2.23	6.12	3.12	3.00
RT01	3.2	2.47	0.73	4.57	2.77	1.8
RT02	1.55	1.36	0.18	2.09	1.55	0.55
RT03	4.15	3.23	0.92	5.92	3.62	2.23
CRT04	3.09	2.09	1.00	6.44	2.15	4.29
CRT06	1.92	1.83	0.08	2.42	2.08	0.33
CRT07	5.77	2.69	3.08	8.15	3.65	4.50
CRT08	2.81	2.35	0.38	2.77	2.31	0.38
CRT09	2.14	1.93	0.21	2.64	2.43	0.21
RT04	1.96	1.88	0.08	3.73	2.50	1.23
<b>Averages</b>	<b>3.06</b>	<b>2.18</b>	<b>0.89</b>	<b>4.40</b>	<b>2.57</b>	<b>1.81</b>
<b>SD</b>	1.38	0.61	0.94	1.91	0.63	1.48
<b>SEM</b>	0.39	0.17	0.27	0.54	0.18	0.42
<b>p-values</b>	<b>0.001</b>	<b>0.002</b>	<b>0.004</b>			

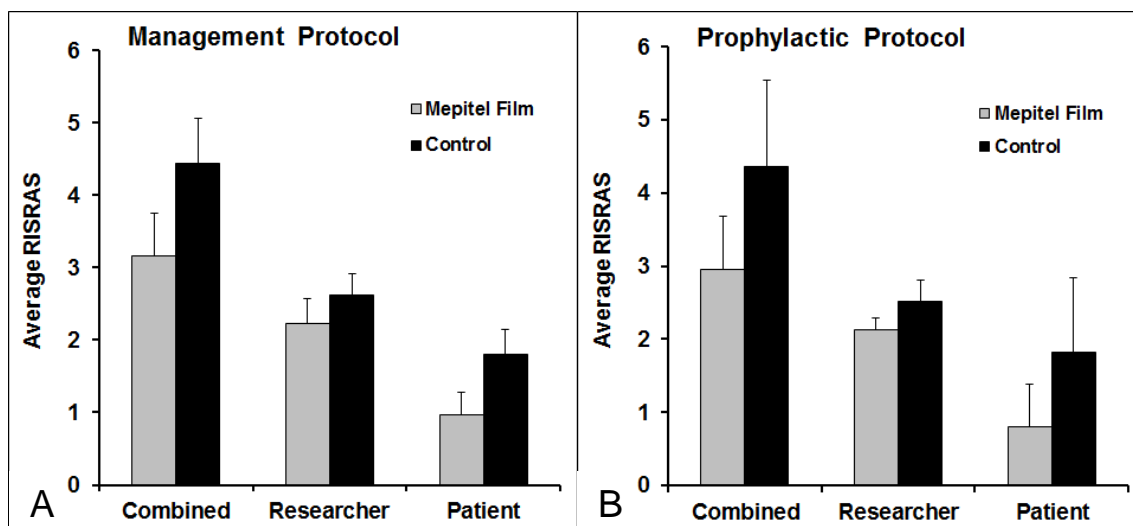
\*Patients in grey were on the management protocol

**Table 3.4 Average scores of the six patients on the management protocol.**

	Average RISRAS scores					
	Mepitel Film			Sorbolene		
	Combined	Researcher	Patient	Combined	Researcher	Patient
<b>Averages</b>	<b>3.17</b>	<b>2.22</b>	<b>0.97</b>	<b>4.44</b>	<b>2.63</b>	<b>1.80</b>
<b>SD</b>	1.43	0.83	0.77	1.52	0.73	0.83
<b>SEM</b>	0.58	0.34	0.31	0.62	0.30	0.34
<b>p-values</b>	<b>0.003</b>	<b>0.029</b>	<b>0.002</b>			

**Table 3.5 Average scores of the six patients on the prophylactic protocol.**

	Average RISRAS scores					
	Mepitel Film			Sorbolene		
	Combined	Researcher	Patient	Combined	Researcher	Patient
<b>Averages</b>	<b>2.95</b>	<b>2.13</b>	<b>0.81</b>	<b>4.36</b>	<b>2.52</b>	<b>1.83</b>
<b>SD</b>	1.46	0.33	1.16	2.38	0.58	2.02
<b>SEM</b>	0.73	0.17	0.58	1.19	0.29	1.01
<b>p-values</b>	<b>0.021</b>	<b>0.023</b>	<b>0.058</b>			

**Figure 3.2 Graphs showing the combined average RISRAS scores for the management (A) and prophylactic (B) cohorts.**

When the results of all patients were combined, there was a statistically significant decrease in skin reaction severity in favour of Mepitel Film of 29% for combined scores, of 15% for researcher scores and of 49% for patients' scores. For patients on the management protocol this decrease in skin

reaction severity was also statistically significant for combined (30%), researcher (16%) and patient (52%) RISRAS scores. For patients on the prophylactic protocol there was a statistically significant reduction in skin reaction severity for the combined (28%) and researcher (14% scores) in favour of Mepitel Film. This decrease was of border line significance for the patient scores (46%). The large variation in patient scores responsible for this lack of statistical significance was due to two patients with moderate skin reactions who reported that Mepitel Film did not make any difference to their skin at all. In such a small cohort this affected the SEM and the p value for the patient RISRAS score. When both management and prophylactic protocol patients were combined this effect was no longer evident. Figure 3.3 and 3.4 show the effect Mepitel had on the skin compared to the Sorbolene area in two patients.



**Figure 1.3 patient CRT07 last day of treatment**



**Figure 3.4 patient CRT09 week 5**

### 3.4.2. Peak RISRAS scores

The peak RISRAS scores refer to the maximum recorded researcher score from any assessment in the study areas. For the majority of patients, the peak score occurred at the end of treatment or in the 1-2 weeks following treatment. The difference in peak RISRAS score between skin covered with Mepitel Film and control skin was significantly different ( $p=0.02$ ) (Student t-test) in favour of Mepitel Film (Table 3.6).

**Table 3.6 Peak Researcher Scores for each patient.**

Patient ID	Peak Researcher RISRAS Score	
	Sorbolene	Mepitel
CRT-01	7.5	4
CRT-02	4.5	2
CRT-03	6.5	6
CRT-04	4	5
CRT-06	6	4
CRT-07	7.5	5
CRT-08	7	8.5
CRT-09	4	3
RT-01	6	3
RT-02	3	2
RT-03	9	9.5
RT-04	9	6.5
Average	6.17	4.88
p value	0.02	



### 3.4.3. Modified RTOG

Table 3.7 displays the peak modified RTOG scores for all trial patients. The clinically most significant difference is between 2 (brisk erythema) and 2.5 (moist desquamation).

**Table 3.7. Peak RTOG scores for each patient.**

Patient ID*	RTOG Peak Score	
	Mepitel	Control
CRT01	2	2.5
CRT02	2	2.5
CRT03	1	2.5
RT01	2	2.5
RT02	1.5	1.5
RT03	3	2.5
CRT04	2.5	2.5
CRT06	2	2
CRT07	2	2.5
RT04	2.5	2.5
CRT08	3	2.5
CRT09	2	2
# with 1 and 1.5	2	1
# with 2	6	2
# with 2.5	2	9
# with 3	2	0

\* Patients in grey were on management protocol

### 3.4.5. Incidence of moist desquamation

The incidence of moist desquamation in the trial areas was assessed in the research areas both by the researcher part of RISRAS (as % of skin area with moist desquamation) and RTOG (level IIB and above) (Table 3.7). Any areas outside of the test areas that developed moist desquamation were not included in any analyses. Overall when RTOG scores are compared between Mepitel Film and control patches for all patients, 4 patients (33%) developed moist desquamation in the Mepitel areas and 9 patients (75%) developed moist desquamation in the control areas.

#### Management protocol

For the management protocol 17% of the Mepitel Film areas (n=1) developed moist desquamation compared to 83% (n=5) of the control areas. The patient that developed moist desquamation in the Mepitel Film area received a slightly higher dose in that area compared to the control area. Patient CRT02 was the only patient where the entire treatment fields were included in the Mepitel Film and control areas. This is because this patient had a low stage of disease so the fields encompassed a very small area.

#### Prophylactic Protocol

For the prophylactic protocol, 50% of the patients developed moist desquamation in the Mepitel Film area (n=3) and 67% of patients in the control areas (n=4).

### 3.4.6. Time to peak skin reaction

The peak reaction was defined as the peak researcher RISRAS score for each patient. The time to the peak reaction was calculated as days from the start of treatment (Table 3.8). For the Mepitel Film areas, the mean time to peak skin reaction was 41.5 days (range 33-48) and 38.1 days (range 27-46) for the Sorbolene control areas. On average, the peak reaction under the Mepitel Film took 3.4 days longer to occur. Using a paired sample two-tailed student t-test, this difference was shown to be statistically highly significant ( $p=0.001$ ).

**Table 3.8 Time in days to the peak reaction for each patient.**

Patient ID	Time to Peak Reactions (Days)	
	Mepitel	Sorbolene
CRT-01	46	46
CRT-02	47	42
CRT-03	46	40
CRT-04	39	35
CRT-06	43	37
CRT-07	33	27
CRT-08	39	35
CRT-09	38	35
RT-01	38	38
RT-02	37	37
RT-03	48	41
RT-04	44	44
<b>Average</b>	<b>41.5</b>	<b>38.1</b>
<b>p-value</b>	<b>0.001</b>	

### 3.5 Stress levels

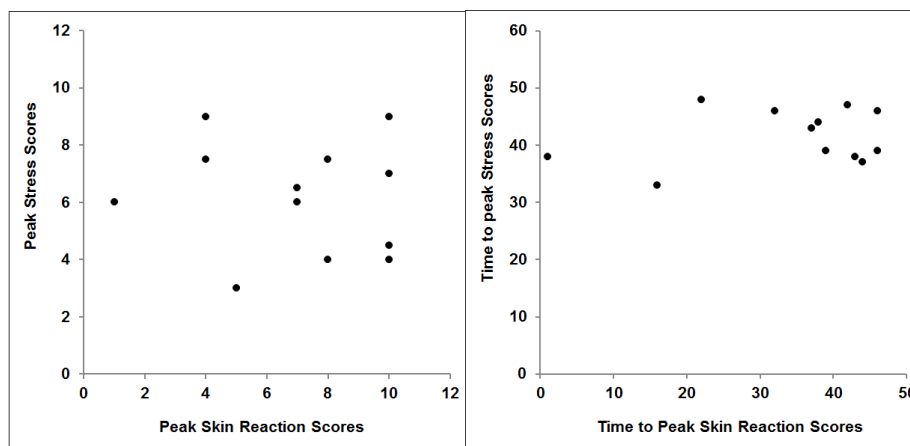
Patient stress levels were measured using the NZ validated Distress Thermometer (DT)(79). Maximum reported stress levels, the stages of the treatment these occurred at, maximum skin reaction severities and the presence of moist desquamation (MD) are reported in Table 3.9. The mean maximum stress score was 7 and the mean time from the start of RT to maximum stress was 43 days. Patient RT-01 reported he did not suffer from stress at any time of his treatment, scoring a 1 for all assessments. Patients CRT-02, CRT-04 and CRT-08 each reported a score of 10, the highest level of stress. The National Comprehensive Cancer Network (NCCN) suggests that the best cut-off point for non-stressed/stressed individuals is 3/4(86). If we follow those guidelines, all but patient RT-01 should be considered stressed and an evaluation of stress on skin reaction severity would not be possible. The one patient who did not consider himself stressed developed MD; whereas patients who scored “5” “7” and “8” did not develop MD.

**Table 3.9 Peak stress and RISRAS scores, time to peak scores and presence of moist desquamation (MD) of control areas of individual patients.**

Patient	Peak stress score	Time to peak stress score (days)	Peak RISRAS *	Time to peak RISRAS (days)	MD
RT-01	1	1	6	38	yes
RT-03	4	22	9	41	yes
CRT-01	4	32	7.5	46	yes
RT-02	5	44	3	37	no
CRT-03	7	46	6.5	40	yes
CRT-06	7	37	6	37	no
CRT-07	8	16	7.5	27	yes
CRT-09	8	43	4	35	no
CRT-02	10	42	4.5	42	yes
CRT-04	10	46	4	35	yes
CRT-08	10	39	7	35	yes
RT-04	10	38	9	44	yes
<b>Average</b>	<b>7.0</b>	<b>34</b>	<b>6.2</b>	<b>38</b>	
SD	3.0	14.0	2.0	5.0	
SEM	0.9	4.0	0.6	1.5	

\* control (Sorbolene) Researcher RISRAS

Plotting maximum stress levels against maximum researcher RISRAS levels (Figure 3.2A), or time to peak stress scores against time to peak RISRAS scores (Figure 3.2B) shows no correlation between stress levels and skin reaction severity.



**Figure 3.2. Lack of correlation between stress levels and skin reaction severity.** A. Correlation between peak scores of individual patients. B. Correlation between time to peak scores of individual patients.

The number of times each area of concern was reported over the study is documented in Table 3.10). The most common concerns were mouth sores (n=35) pain (n=31) and fatigue (n=30). Patients also commented on 'other' areas not listed on the stress thermometer. These included having to wear a mask during treatment, throat pain, vomiting, moving house, coughing, swallowing and being in hospital. Three patients commented on their frustrations with treatment. Six patients were admitted to hospital for various reasons, including nausea, hydration, chest infection, bilateral pulmonary emboli, neutropenic sepsis and low platelet count.

**Table 3.10 Areas of concern for patients that contributed to their perceived distress.**

Domains	Area of concern	Times reported
<b>Spiritual</b>		0
<b>Practical</b>	Child care	0
	Housing	0
	Financial	1
	Transportation	1
	Work/school	4
	Cultural obligations	0
	Hospital processes	1
<b>Family</b>	Dealing with children	6

	Dealing with partner	12
	Other family members	4
	Family dealing with the situation	5
<b>Emotional</b>	Depression	5
	Fears	9
	Anxiety	12
	Sadness	5
	Worry	11
	Loss of interest in usual activities	15
<b>Physical</b>	Appearance	3
	Bathing/dressing	1
	Breathing	3
	Urination	2
	Constipation	12
	Diarrhoea	12
	Eating	33
	Fatigue	30
	Feeling swollen	3
	Fevers	2
	Getting around	3
	Indigestion	1
	Memory/concentration	5
	Mouth sores	35
	Nausea	18
	Dry nose/congested	9
	Pain	31
	Sexual	1
	Skin dry/itchy	12
	Sleep	8
	Tingling hands/feet	1
<b>Other</b>	Mask	1
	Mask+waiting for treatment	1
	Coughing	1
	Vomiting	1
	Pain in tongue	1
	Moving house	1
	Being in hospital, swallowing	1
	Frustrated with treatment, secretions	1
	Throat phlegm and cramps	1
	Anger and frustration	1

	Not being able to be my normal self is frustrating	1
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### 3.6 Exit questionnaires

Each patient was given an exit questionnaire to give them the opportunity to describe their experience of being in the trial and using Mepitel Film and Sorbolene on their skin at the end of the follow-up period. A total of 11 out of 12 patients returned the questionnaire.

#### Trial experience

Ten patients answered the question about whether being in the trial was a positive experience or not with “yes”. The patient who answered this question with “no”. Five patients commented about their experience, with a clear theme of altruism as a reason for participating.

*“good to know it may make a difference to someone”- CRT04*

*“happy to help”- RT01*

*“good to be seen weekly’ by the research assistant”- CRT09*

*“yes it was a positive experience”- CRT01*

*“yes Hayley (the research assistant) is very competent”- CRT07*

It appeared that the patients appreciated being seen by a designated person, as the research assistant often helped the patient with side effects other than skin reactions.

#### Managing skin reactions

When asked whether Mepitel was better than Sorbolene in managing their skin reactions, nine out of 11 patients answered that they thought the Mepitel Film was better than the cream. The remaining two patients did not answer this question. Two patients commented that the Mepitel Film helped reduce itching and irritation and one patient commented that there was less skin flaking under the Mepitel Film.

Mepitel helped “stop the itching and irritation’ – CRT02

*“Yes the Mepitel was better than the cream. The reaction was less severe under the dressing”- CRT03*

In the management group patients commented that the Mepitel Film helped more during the treatment, but during the follow-up period the cream patch seemed to heal faster.

*“At the peak of the treatment when it was burning the film was good but when the other side has healed the film side is itchy and worse” – CRT01 and another said ‘possibly, however the Sorbolene was very good at soothing the skin reaction and seem to be better at the end; ie Sorbolene side recovered faster”- RT01*

### Advantages of Mepitel Film

When asked about what were the advantages of using Mepitel Film, all 11 patients answered this question. The patients commented on the ease of use and comfort of the Mepitel Film.

*“There was no burning, stinging or itching”- CRT04*

*“didn’t get the burning feeling like the rest of my neck” - RT04*

Two patients commented that Mepitel Film was better at the beginning of their treatment.

*“Mepitel was good at the peak of burning but after that it was too itchy”- CRT01*

*“Mepitel seems to be better at the beginning” – RT01*

### Disadvantages of Mepitel Film

When asked about the disadvantages of using Mepitel Film, nine patients answered this question. The majority of patients agreed that the Mepitel Film often came off easily and rolled at the edges, which was annoying to them.

*“Only slightly annoying when it wouldn’t stay on. Appearance not an issue for me”- RT01*

Patient CRT02 commented during the treatment that he was asked by work colleagues ‘why he had glad wrap on his face’. The patient however stated he was not bothered by these questions.

One patient commented that Mepitel Film had

*“delayed healing”- RT03*



Another patient felt that the disadvantage was that he didn't get to use the Mepitel Film everywhere.

*"....more comfortable – didn't get the other symptoms like the rest of my neck- would have liked Mepitel over the whole neck"- RT04*

### **Taking part in other clinical trials in the future**

Ten patients said they would be happy to take part in future clinical trial based on their experience with this trial. Again the theme of altruism was noted, with patients commenting

'yes- anything to help people feel more comfort for what they are going through' -CRT04

and

'yes I would because it's helping other people.' – RT04

### **Results of the trial**

Seven patients wanted the results of the trial sent to them.

## Chapter 4 Discussion

The aim of this randomised controlled feasibility study was to investigate whether Mepitel Film dressings were superior to Sorbolene cream in reducing or managing radiation-induced skin reactions in patients with head and neck cancer. Based on previous studies in breast cancer patients (10), it was hypothesised that Mepitel Film would protect the irradiated skin from friction and thus further damage. This thesis has analysed the skin reactions of first 12 patients of a larger feasibility trial and includes six patients on the management protocol and six patients on the prophylactic protocol at the CRCHS. The feasibility study is now closed for further recruitment in NZ and is still recruiting in China.

Mepitel Film was tested against Sorbolene cream. This is not the standard of care at CRCHS, which instead uses Fatty E cream. Fatty E cream and Sorbolene cream are similar emollients and neither contain sodium lauryl sulphate, which has been shown to thin the skin (62,63). Sorbolene cream was chosen based on the review by Kumar et al., as it is a common emollient used throughout Australia and New Zealand (9). Emollient creams are also recommended by over 70% of departments who responded to their survey, so using Sorbolene cream was therefore considered a clinically relevant control cream. None of the patients experienced any adverse events due to Mepitel Film. Mepitel did not cause any allergic skin reaction for any of the participants.

A discussion of the key findings is provided below, followed by a discussion of limitations and suggestions for future research.

### 4.1 Skin reaction severity

Based on the theory that Mepitel Film is a completely inert dressing, which closely adheres to the skin to provide protection against friction, it could be assumed that the sooner Mepitel Film is applied, the better it works. This theory can be substantiated when comparing the moist desquamation (MD) incidences between the prophylactic Mepitel Film trial by Herst et al. (10), the No-Sting Barrier Film by Graham et al. (74) and the management Mepilex Lite trial by Paterson et al. (42). Herst et al. used Mepitel Film in both mastectomy (n=44) and non-mastectomy (n=34) breast cancer patients from the start of radiation therapy and found an overall decrease in skin reaction severity of over 90% in the Mepitel Film patches (using combined RISRAS) and no MD underneath Mepitel Film patches at all,

compared with MD rates in control patches of 27% (10). Graham et al. found a reduced rate of moist desquamation in their mastectomy cohort, with 33% for the No-Sting Barrier Film vs 46% for sorbolene ( $p=0.096$ ) and for all patients with area under the curve skin toxicity using RTOG was reduced (8.1 vs 9.2,  $p=0.005$ ). They also got patients to score pruritus and pain on a 5 point Likert scale, with a significant change favouring No-Sting Barrier Film for pruritus (area under the curve,  $p=0.011$ ). In sharp contrast, Paterson et al. who used Mepilex Lite from the moment erythema was visible in 74 post-mastectomy patients reported an overall decrease in skin reaction severity of 40% but no statistically significant difference between MD rates of skin covered in Mepilex Lite and skin covered in control cream. This trial was conducted in four different centres and reported an average MD rate over all four centres of 47% (42). The superior results of the prophylactic trial over the management trial are due to a number of factors:

- Friction protection is going to be most useful when used prophylactically rather than wait till radiation damage to the skin is obvious (when erythema is visible). Hence MD rates in prophylactic trials should always be lower than in management trials if the intervention works by providing friction protection.
- Total dose to the skin is arguably the most important determinant of skin reaction severity, with friction protection less likely to prevent MD at higher skin doses up to the point that the total dose becomes lethal to the basal skin cells and MD is unavoidable. Average skin doses for patients in the prophylactic Mepitel Film breast trial(10) ranged from 30Gy to 39Gy (depending on location) for patients on the conventional regimen (MD 41%) and between 24Gy and 30Gy for patients on the hypo-fractionated regimen (MD 17%). The lower skin dose resulted in a lower MD rate in this trial.

The trials used different dressings. Cavilon No-Sting Barrier Film contains an organosilicon compound that starts as a liquid but becomes a film on contact. Mepitel Film and Mepilex Lite both have a soft silicone contact layer (Safetac technology) which mediates the friction protection of these dressings. Mepitel Film is thinner and transparent and sticks better, can be left on during radiation and thus can be used in a prophylactic setting. Mepilex Lite is thicker with a thin non-transparent foam layer on top of the silicon contact layer and needs to be removed during radiation. It could be that Mepitel Film would provide better protection from friction because it conforms better to the folds of the skin and is more likely to stay on the skin for longer, before needing to be replaced.

In light of the breast cancer trial results, the results of the 12 head and neck cancer patients analysed for this thesis were very interesting and not altogether unexpected because of the higher skin dose and the different patient cohorts. The skin reaction severity results are discussed below.

### **1. Mepitel Film reduced skin reaction severity**

Mepitel Film reduced the combined, researcher and patient components of RISRAS for patients in both the management and prophylactic protocols. This decrease in skin reaction severity was statistically significant for differences in RISRAS scores of patients on the management trial (p values of 0.001, 0.002 and 0.004 respectively) and statistically significant for the combined and researcher component and trending towards significance for patients on the prophylactic protocol apart (p values of 0.021, 0.023 and 0.058 respectively). Skin reactions peaked on average 38 days after the start of radiation therapy for control patches and after 41.5 days for Mepitel Film patches. This compares well with skin reaction peak times reported by the prophylactic Mepitel Film breast trial (35 days) (10) and the management Mepilex Lite breast trial I (40 days) (42). Although significant, the decrease in skin reaction severity (and hence the amount of protection provided by) Mepitel Film was disappointing (decrease in combined RISRAS of 29%) compared to the decrease reported in breast cancer patients (91%).

### **2. Patients liked Mepitel Film**

The patients, who scored the extent of pain, burning itchiness and effect on daily life, rated Mepitel Film higher (50% decrease) than the researcher (16% decrease) who scored the visible skin reactions (erythema and desquamation). Because the patient and researcher component contribute equally to the combined (overall) RISRAS score, the patient component has a very large impact on the overall skin reaction score (29% decrease). The breast management trial by Paterson et al also documented a stronger positive score from the patients (66% decrease) compared to that of the researchers (28% decrease), resulting in an overall decrease for Mepilex Lite of 41%. One could argue that the driving force behind running radiation-induced skin trials is to find the best way to prevent or manage skin reactions because they affect patient quality of life. The patient component is part of assessing the effect of the dressings on patient quality of life and as such carries a certain amount of weight in these trials. In support of this, patients mentioned in the exit questionnaire that “Mepitel ‘didn’t get the burning feeling like the rest of my neck” (RT04).

### **3. Skin reaction severity was similar between management and prophylactic protocols**

Moist desquamation rates for Mepitel Film patches were lower for management protocol patients than prophylactic protocol patients (17% and 50% respectively). In contrast, control moist desquamation rates were higher for management protocol patients than prophylactic protocol patients (83% and 67% respectively). Care must be taken with interpreting these findings as both of

these cohorts were very small. However the trends discussed here for the 12 patient cohort are the same as for the slightly larger feasibility trial. The results indicate that there is no obvious benefit in applying Mepitel Film from the start of radiation therapy compared with applying it when erythema has developed.

Does this mean that the protective effect of Mepitel Film is lost in the first few weeks of radiation therapy before erythema develops? Perhaps this question is best answered by a careful scrutiny of the head and neck cohort, which consisted of nine men and three women. Early on in the study it became very clear that the continued growth of stubble on the men's necks prevented Mepitel Film from adhering to the folds of the neck. Although silicone based adhesives have many contact points even over uneven surfaces (87), dryness, sweating and hair in the area does affect their adhesion (87). As epilation occurs at approximately the same time as erythema develops (21), it is likely that the protection of Mepitel Film was non-existent during the first few weeks of radiation therapy for these men, explaining the lack of difference in skin reaction severity in the prophylactic and management protocols. The review by Russi et al. also mentioned that Mepitel Film may be difficult to use in head and neck cancer patients, due to the increase in skin folds in this area (7). In addition, the only woman on the prophylactic protocol had greater benefit from Mepitel (25% decrease in researcher RISRAS) than the two women on the management protocol (9% and 3% decrease in researcher RISRAS). The numbers of females in the study is too small to do a meaningful subgroup analysis of these patients. Recruiting females into a head and neck study is difficult as men dominate this cohort with a male to female ratio of 4 according to the New Zealand Cancer Registry (88). Although a previous study has reported that female patients are at greater risk of severe radiation toxicity (38), a larger study with more patients is required to validate this using Mepitel Film.

#### **4. Head and neck patients have a higher incidence of moist desquamation.**

Moist desquamation rates for controls in both the prophylactic (67%) and management (83%) protocols were higher than those reported for the breast cancer trials (26% and 47% in prophylactic and management protocols).(10,42)

Taken together, these results show that Mepitel Film is less effective in head and neck cancer patients than in breast cancer patients. The most likely explanation is that the skin dose in head and neck patients was much higher compared with breast cancer patients. The average skin doses were 51Gy for Mepitel Film skin patches (52Gy for management protocol and 50Gy for prophylactic protocol) and 49.4Gy for control patches (50 for management protocol and 48.5Gy for prophylactic protocol). These

differences between Mepitel Film and control patches and management and prophylactic protocols were not statistically significant and are unlikely to have contributed to any differences in moist desquamation rates or overall skin reaction severity. However, these skin doses are a lot higher than for the prophylactic Mepitel Film breast trial(10) with average skin doses less than 40Gy, which will have contributed to the higher moist desquamation rates in the controls. The substantially higher dose may also have contributed to the higher desquamation rates in the Mepitel Film skin patches. It is possible that these higher doses cause too much damage to the skin and that protection against additional friction is less effective than at lower doses where the skin is able to repair itself in the absence of additional friction damage. A clear dose response relationship between skin reaction severity and dose to the skin has been described previously (23).

The skin area in the neck may also be tougher than skin in the breast/chest area because it is more exposed to the weather and possibly dryer and more wrinkled in older patients (average age in 59 years: range 40-83 years). In addition, regular shaving will “toughen” the skin. Perhaps the protective effect of Mepitel Film is not as pronounced in tougher skin that is exposed to friction from clothing. However, skin in the neck may be more prone to moist desquamation because of the stretching of the skin to accompany movement of the head. In the previous Mepitel Film trial, most MD occurred in areas of increased moisture and friction such as the axilla and inframammary skin folds (10). Skin of the head and neck area is also far more likely to have experienced previous sun exposure than the breast. A study using reflective spectrophotometry however showed that areas of higher sun exposure just showed higher baseline erythema readings compared to irradiated sites and not the highest change in erythema readings (89), whereas Porock et al. hypothesised that UV radiation thins the epidermal layer of the skin or can impair the inflammatory phase of healing (16).

Other studies have reported Grade 3 or higher skin reactions for head and neck cancer patients planned using IMRT as low as 7.5%(24,27). These reports however did not discuss the absolute rate of moist desquamation in their patients but rather used the RTOG scale. Grade 2 on the RTOG scale can be brisk erythema or patchy moist desquamation so just reporting levels of grade 3 skin reactions does not provide a comprehensive evaluation of skin reaction severity. A retrospective analysis of 104 head and neck cancer patients by Givens and colleagues recorded grade 3-4 skin reactions as between 25.7% and 29.6% depending on the IMRT protocol used (90). Only two patients (16.7%) in this study developed grade 3 skin reactions, which is consistent with the above literature.

## 4.2 Stress levels

An interesting finding from the Mepitel Film breast cancer trial was that women who were more highly stressed had more severe skin reactions.<sup>(91)</sup> At every assessment (3x a week), women were asked a standard set of questions about how they were feeling, sleeping, eating, hydrating, managing family, work and other aspects of their lives such as their perceived stress levels. A simple LIKERT scale was used to score patients from 1 (very well) to 5 (not well at all). A highly stressed person was defined as someone with three scores of 5 for each of at least two questions. Using these criteria, 20 patients (26%) of the predominantly female breast cohort (n=78) were deemed stressed and a comparison of RISRAS scores between the stressed and non-stressed cohorts showed significantly worse (2x) skin reactions in the stressed cohort, with a 5x higher change of developing moist desquamation.<sup>(91)</sup> In this trial the researcher wanted to assess if stress was a contributing factor in the predominantly male head and neck cancer cohort. Instead of using a non-validated stress measure, this trial used the validated NZ Distress Thermometer <sup>(79)</sup>. Interestingly, if the NCCN guidelines for analysis of Distress Thermometer data are followed, all but one of the patients in this cohort were stressed and the only patient who did not consider himself stressed at all, developed moist desquamation. Three of the stressed patients did not develop moist desquamation. Correlational analysis showed no direct correlation between stress levels and skin reaction severity in this head and neck cohort.

The areas for concern for these patients were all related to oral mucositis: mouth sores (35 times) problems with eating (33 times) and pain in the oral cavity (31 times). Skin dry/itchy was only reported 12 times. Patients in this trial were often hospitalised for chest infections, pulmonary emboli or hydration and pain issues. This is consistent with a trial by Givens et al., where 97.1% of head and neck patients developed oral mucositis compared to 25.7% developing moist desquamation using IMRT<sup>(90)</sup>. In their study, 25.7% of patients developed severe dehydration or malnutrition and the same number developed severe nausea and vomiting. Although skin reactions have been reported to be distressing for breast cancer patients <sup>(92)</sup>, head and neck cancer patients have much more challenging side effects that can contribute to their perceived stress. Although one could argue that managing skin reactions may not be as important as managing oral mucositis as it was reported less often by this patient cohort, one could also say that finding an easy way to decrease skin reaction severity at least helps that aspect of their lives and would go a small way to improving their quality of life.

### 4.3 Limitations

The main limitation of this trial is the unavoidable lack of blinding because the intervention is a film and the control is a cream. This may have caused some researcher and participant bias when assessing skin reaction severity. When asking patients to assess the Sorbolene control and Mepitel Film areas, some patients found it difficult to differentiate between the two areas. Due to the complex nature and rapid dose falloff of IMRT and VMAT plans, the control and Mepitel Film areas were often chosen on the same side of the neck, as the opposite side tended to have a different dose depending on the site of diagnosis. It was not possible like the breast cancer trial to completely separate the treatment field into two equal halves for most patients. Patients would often comment on how the contralateral side of their neck felt rather than the same side.

Other limitations included:

- The study areas did not include the entire treated area, due to the complex nature of VMAT and IMRT plans. One patient had a 3DCRT plan that were able to be divided into equal halves for the study and made assessing the area for both the research assistant and the patient much easier. For the other patients, the side of the neck with the most even dose according to the planning system was chosen, meaning the study areas were not necessarily the area of highest dose. This made it difficult for patients to differentiate how their skin felt and may have influenced the patient component of the RISRAS scores.
- The initial skin assessment was subject to recall and reporter bias. Patients were questioned about their past medical history and lifestyle. It is possible that some will under-report certain lifestyle choices, such as smoking, as there is a stigma associated with this. The research assistant used the patients' oncology notes to verify information wherever possible. In the oncology notes two patients who had previously told the research assistant they were non-smokers had in fact only just decided to quit so had actually been smoking until that time.
- Potential lack of compliance. Adherence to the trial protocol was difficult to assess. Patients were instructed to apply Sorbolene Cream to the control area twice daily throughout their treatment and follow-up time. Measuring compliance was not possible in this context, although all patients insisted they were following the trial instructions. For many patients, the Mepitel Film fell off during the night for the first few weeks of treatment, especially those on the prophylactic trial. It would have been possible therefore for the patients to accidentally apply the Sorbolene cream to the Mepitel Film area before it was replaced by the research



assistant. It was easy to establish whether or not Mepitel Film was removed or had fallen off as patients cannot reapply it once it has come off.

- The cohort was very small (12 patients). A potential problem with small cohorts is that one patient can have a significant effect on the average outcomes. For example patient CRT07 had a much higher RISRAS score than the other patients on the trial, (combined score for the Film was 5.77, combined score for the Sorbolene was 8.15) which would have increased the average severity score as well as the SD and SEM. However, even in this 12 patient cohort the difference in skin reaction severity and peak reaction scores between Mepitel Film and cream were still statistical significant.
- Gender bias: This study also recruited far more males (9) than females (3) and this is a reflection of the gender distribution for H&N cancer patients in NZ (84). Recruiting more women was beyond the resources of this trial.
- Location bias. Only patients from Canterbury were recruited because they could attend four weekly follow-up appointments. Thirteen patients who were screened were excluded based on this. Being able to remotely see patients via video conference would have meant these patients could have been included in the trial without prolonging the recruitment period.

## 5. Conclusions and future directions

Radiation-induced skin reactions are a common occurrence during radiation therapy treatment for head and neck cancer patients. There is a lack of evidence supporting the use of any one topical agent for the reduction of skin reactions, particularly for this cohort of patients.

This honours thesis reports and analyses the results of the first 12 patients of a feasibility study that will include 30 patients from two New Zealand centres and one Chinese centre. The aim of this randomised controlled feasibility study was to investigate whether Mepitel Film dressings were superior to Sorbolene cream in reducing or managing radiation-induced skin reactions in patients with head and neck cancer.

Even within the small sub-cohort in this thesis it appears that this cohort does not respond to Mepitel Film in the same way breast cancer patients do. The significantly higher dose to the skin of head and neck patients may mean that protection against friction will never completely prevent MD. Issues with beard growth pushing the film away from the skin surface and tougher skin in the neck area have all been identified as barriers to using Mepitel Film for these patients, particularly in a prophylactic setting.

However, the Mepitel Film did offer some protection: even in this small cohort the differences in RISRAS measures between intervention and control skin areas did reach statistical significance, even if the protection is of a small size (30% rather than 90% in breast cancer patients).

Using VMAT to deliver radiation therapy may decrease the skin dose to the extent that Mepitel Film may achieve improved results. This will be further explored in the analysis of the larger feasibility study.

Although radiation-induced skin reactions do contribute to reductions in quality of life, patients with cancer of the head and neck experience several other side effects that can exacerbate their levels of stress. There is no evidence however in this small cohort of patients that stress levels have an effect on the severity of radiation-induced skin reactions.

Preliminary results from the Chinese cohort of nasopharyngeal cancer patients (n=11), suggest that prophylactic use of Mepitel Film has a stronger protective effect than in the NZ cohort. The Chinese cohort of mainly men receive bilateral 50Gy/25# to cover the neck nodes with a skin dose between 35 and 45 Gy. In addition, Chinese men do not have full or heavy beards and they did not experience problems with the Mepitel Film coming off in the first weeks of treatment. The few women in the NZ trial seemed to derive more benefit from Mepitel Film, so further studies in female head and neck patients would be useful as well, even though recruitment will be slow as women make up such a small fraction of the head and neck cohort.

It appears that Mepitel Film tends to protect sub-lethally damaged skin from friction damage but for it to be effective it needs to adhere closely to the skin and the dose cannot be over 40Gy. These feasibility studies are useful because they identify cohorts for which the Mepitel Film is most likely to work.

## References

1. Group NH and NCTSW. Standards of Service Provision for Head and Neck Cancer Patients in New Zealand - Provisional. Wellington; 2013.
2. Elwood JM, Youlden DR, Chelimo C, Ioannides SJ, Baade PD. Comparison of oropharyngeal and oral cavity squamous cell cancer incidence and trends in New Zealand and Queensland, Australia. *Cancer Epidemiol* [Internet]. Elsevier Ltd; 2014;38(1):16–21. Available from: <http://dx.doi.org/10.1016/j.canep.2013.12.004>
3. Gregoire V, Lefebvre J-L, Licitra L, Felip E. Squamous cell carcinoma of the head and neck: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* [Internet]. 2010;21(Supplement 5):v184–6. Available from: <http://annonc.oxfordjournals.org/cgi/doi/10.1093/annonc/mdq185>
4. Noble-Adams R. Radiation-induced reactions 2: development of a measurement tool. *Br J Nurs*. 1999;8(18):1208–11.
5. Hughes a, Mitchell a, Bianchini J, Al E. Care of radiation skin reactions. BC Cancer Agency. 2006;(March):1–17.
6. Wells M, MacBride SM. Radiation skin reactions. *Support care Radiother* [Internet]. 2003;135–59. Available from: <http://www.eu.elsevierhealth.com/media/us/samplechapters/9780443064869/9780443064869.pdf>
7. Russi EG, Moretto F, Rampino M, Benasso M, Bacigalupo A, De Sanctis V, et al. Acute skin toxicity management in head and neck cancer patients treated with radiotherapy and chemotherapy or EGFR inhibitors: Literature review and consensus. *Crit Rev Oncol Hematol* [Internet]. Elsevier Ireland Ltd; 2015;96(1):167–82. Available from: <http://dx.doi.org/10.1016/j.critrevonc.2015.06.001>
8. Chan RJ, Webster J, Chung B, Marquart L, Ahmed M GS. Prevention and treatment of acute radiation-induced skin reactions: a systematic review and meta-analysis of randomized controlled trials. *BMC Cancer*. 2014;14:53.
9. Kumar S, Juresic E, Barton M, Shafiq J. Management of skin toxicity during radiation therapy: A review of the evidence. *J Med Imaging Radiat Oncol*. 2010;54(3):264–79.
10. Herst PM, Bennett NC, Sutherland AE, Peszynski RI, Paterson DB, Jasperse ML. Prophylactic use of Mepitel Film prevents radiation-induced moist desquamation in an intra-patient randomised controlled clinical trial of 78 breast cancer patients. *Radiother Oncol*. 2014;110(1):137–43.
11. FitzGerald TJ, Jodoin MB, Tillman G, Aronowitz J, Pieters R, Balducci S, et al. Radiation Therapy Toxicity to the Skin. *Dermatol Clin*. 2008;26(1):161–72.
12. Hopewell J. The skin: its structure and response to ionizing radiation. *Int J Radiat Biol*. 1990;57(4):751–73.
13. Harper JL, Franklin LE, Jenrette JM, Aguero EG. Skin toxicity during breast irradiation: pathophysiology and management. *South Med J* [Internet]. 2004;97(10):989–93. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15558927>

14. Stone HB, Coleman CN, Anscher MS, McBride WH. Reviews Effects of radiation on normal tissue : consequences and mechanisms. 2003;529–36.
15. Herst PM. Protecting the radiation-damaged skin from friction: A mini review. *J Med Radiat Sci.* 2014;61(2):119–25.
16. Porock D. Factors influencing the severity of radiation skin and oral mucosal reactions: Development of a conceptual framework. *Eur J Cancer Care (Engl).* 2002;11(1):33–43.
17. Waghmare CM. Radiation burn - From mechanism to management. *Burns* [Internet]. Elsevier Ltd and International Society of Burns Injuries; 2013;39(2):212–9. Available from: <http://dx.doi.org/10.1016/j.burns.2012.09.012>
18. Morgan K. Radiotherapy-induced reactions : prevention and cure. *Br J Nurs.* 2014;23(16):S25–32.
19. Noble-Adams R. Radiation-induced reactions. 1: An examination of the phenomenon. *Br J Nurs.* 1999;8(17):1134–40.
20. Archambeau J, Penzer R, Wasserman T. Pathophysiology of irradiated skin and breast. *Int J Radiat Oncol Biol Phys.* 1995;31(5):1171–85.
21. Hymes S, Strom E, Fife C. Radiation dermatitis: Clinical presentation, pathophysiology, and treatment 2006. *J Am Acad Dermatol.* 2006;54(1):28–46.
22. Palatty PL, Azmidah a., Rao S, Jayachander D, Thilakchand KR, Rai MP, et al. Topical application of a sandal wood oil and turmeric based cream prevents radiodermatitis in head and neck cancer patients undergoing external beam radiotherapy: A pilot study. *Br J Radiol.* 2014;87(1038):1–10.
23. Porock D, Kristjanson L, Nikoletti S, Cameron F, Pedler P. Predicting the severity of radiation skin reactions in women with breast cancer. [Internet]. Vol. 25, *Oncology nursing forum.* 1998. p. 1019–29. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/9679261>
24. Spiotto MT, Weichselbaum RR. Comparison of 3D conformal radiotherapy and intensity modulated radiotherapy with or without simultaneous integrated boost during concurrent chemoradiation for locally advanced head and neck cancers. *PLoS One.* 2014;9(4).
25. Isbruch AVE, Arris JOH, Arden ADAMSG, Hao CLKSC, Traube WIS, Arari PAULMH, et al. Head and Neck multi-institutional trial of accelerated hypofractionated intensity-modulated radiation therapy for early-stage oropharyngeal cancer ( RTOG 00-22 ). 2010;76(5):1333–8.
26. Teh B., Woo S., Butler E. Intensity Modulated Radiation Therapy: A New Promising Technology in Radiation Oncology. *Oncologist* [Internet]. 1999;4(6):433–42. Available from: <http://theoncologist.alphamedpress.org/content/4/6/433.full>
27. Gupta T, Agarwal J, Jain S, Phurailatpam R, Kannan S, Ghosh-Laskar S, et al. Three-dimensional conformal radiotherapy (3D-CRT) versus intensity modulated radiation therapy (IMRT) in squamous cell carcinoma of the head and neck: A randomized controlled trial. *Radiother Oncol* [Internet]. Elsevier Ireland Ltd; 2012;104(3):343–8. Available from: <http://dx.doi.org/10.1016/j.radonc.2012.07.001>
28. Yom SS, Yuen F, Tang J. Skin Care in Radiation Oncology. In: Fowble B, Yom SS, Yuen F, Arron S, editors. *Skin Care in Radiation Oncology.* Springer International Publishing; 2016.

29. Sharp L, Lewin F, Johansson H, Payne D, Gerhardsson A, Rutqvist LE. Randomized trial on two types of thermoplastic masks for patient immobilization during radiation therapy for head-and-neck cancer. *Int J Radiat Oncol Biol Phys*. 2005;61(1):250–6.
30. Lee N, Chuang C, Quivey JM, Phillips TL, Akazawa P, Verhey LJ, et al. Skin toxicity due to intensity-modulated radiotherapy for head-and-neck carcinoma. *Int J Radiat Oncol Biol Phys*. 2002;53(3):630–7.
31. Giro C, Berger B, B?lke E, Ciernik IF, Duprez F, Locati L, et al. High rate of severe radiation dermatitis during radiation therapy with concurrent cetuximab in head and neck cancer: Results of a survey in EORTC institutes. *Radiother Oncol* [Internet]. Elsevier Ireland Ltd; 2009;90(2):166–71. Available from: <http://dx.doi.org/10.1016/j.radonc.2008.09.007>
32. Pryor DI, Porceddu S V., Burmeister BH, Guminiski A, Thomson DB, Shepherdson K, et al. Enhanced toxicity with concurrent cetuximab and radiotherapy in head and neck cancer. *Radiother Oncol* [Internet]. Elsevier Ireland Ltd; 2009;90(2):172–6. Available from: <http://dx.doi.org/10.1016/j.radonc.2008.09.018>
33. Studer G, Brown M, Salgueiro EB, Schmückle H, Romancuk N, Winkler G, et al. Grade 3/4 dermatitis in head and neck cancer patients treated with concurrent cetuximab and IMRT. *Int J Radiat Oncol Biol Phys*. 2011;81(1):110–7.
34. Dasari S, Bernard Tchounwou P. Cisplatin in cancer therapy: Molecular mechanisms of action. *Eur J Pharmacol* [Internet]. Elsevier; 2014;740:364–78. Available from: <http://dx.doi.org/10.1016/j.ejphar.2014.07.025>
35. Palazzi M, Tomatis S, Orlandi E, Guzzo M, Sangalli C, Potepan P, et al. Effects of Treatment Intensification on Acute Local Toxicity During Radiotherapy for Head and Neck Cancer: Prospective Observational Study Validating CTCAE, Version 3.0, Scoring System. *Int J Radiat Oncol Biol Phys*. 2008;70(2):330–7.
36. Sandby-Møller J, Poulsen T, Wulf HC. Epidermal Thickness at Different Body Sites: Relationship to Age, Gender, Pigmentation, Blood Content, Skin Type and Smoking Habits. *Acta Derm Venereol*. 2003;83(6):410–3.
37. Giacomoni PU, Mammone T, Teri M. Gender-linked differences in human skin. *J Dermatol Sci*. 2009;55(3):144–9.
38. Meyer F, Fortin A, Wang C, Liu GEL, Bairati ISB. Predictors of severe acute and late toxicities in patients with localised head-and-neck cancer treated with radiation therapy. *Int J Radiat Oncol Biol Phys*. 2012;82(4):1454–62.
39. Dehing-Oberije C, De Ruyscher D, Petit S, Van Meerbeeck J, Vandecasteele K, De Neve W, et al. Development, external validation and clinical usefulness of a practical prediction model for radiation-induced dysphagia in lung cancer patients. *Radiother Oncol* [Internet]. Elsevier Ireland Ltd; 2010;97(3):455–61. Available from: <http://dx.doi.org/10.1016/j.radonc.2010.09.028>
40. Ulf E, Maroti M, Serup J, Falkmer U. A potent steroid cream is superior to emollients in reducing acute radiation dermatitis in breast cancer patients treated with adjuvant radiotherapy. A randomised study of betamethasone versus two moisturizing creams. *Radiother Oncol* [Internet]. Elsevier Ireland Ltd; 2013;108(2):287–92. Available from: <http://dx.doi.org/10.1016/j.radonc.2013.05.033>

41. Ryan JL, Bole C, Hickok JT, Figueroa-Moseley C, Colman L, Khanna RC, et al. Post-treatment skin reactions reported by cancer patients differ by race, not by treatment or expectations. *Br J Cancer* [Internet]. 2007;97(1):14–21. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2359663&tool=pmcentrez&rendertype=abstract>
42. Paterson DB, Poonam P, Bennett NC, Peszynski RI, Van Beekhuizen MJ, Jasperse ML, et al. Randomized intra-patient controlled trial of mepilex lite dressings versus aqueous cream in managing radiation-induced skin reactions post-mastectomy. *J Cancer Sci Ther*. 2012;4(11):347–56.
43. Guo S, Dipietro L a. Factors affecting wound healing. *J Dent Res* [Internet]. 2010;89(3):219–29. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20139336>
44. Turesson I, Nyman J, Holmberg E, Oden A. Prognostic factors for acute and late skin reactions in radiotherapy patients. *Int J Radiat Oncol Biol Phys*. 1996;36(5):1065–75.
45. Sharp L, Johansson H, Hatschek T, Bergenmar M. Smoking as an independent risk factor for severe skin reactions due to adjuvant radiotherapy for breast cancer. *Breast* [Internet]. Elsevier Ltd; 2013;22(5):634–8. Available from: <http://www.sciencedirect.com/science/article/pii/S0960977613002129>
46. Alapetite C, JM C, MH B, Masse R. Genetic susceptibility to radiations Which impact on medical practice ? *Q J Nucl Med*. 2000;44(4):347–54.
47. Christian LM, Graham JE, Padgett D a., Glaser R, Kiecolt-Glaser JK. Stress and wound healing. *Neuroimmunomodulation*. 2007;13(5–6):337–46.
48. Chen Y, Lyga J. Brain-skin connection: stress, inflammation and skin aging. *Inflamm Allergy Drug Targets*. 2014;13(3):177–90.
49. Ebrecht M, Hextall J, Kirtley LG, Taylor a, Dyson M, Weinman J. Perceived stress and cortisol levels predict speed of wound healing in healthy male adults. *Psychoneuroendocrinology* [Internet]. 2004;29(6):798–809. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15110929>
50. Kong M, Shin SH, Lee E, Yun EK. The effect of laughter therapy on radiation dermatitis in patients with breast cancer: A single-blind prospective pilot study. *Onco Targets Ther*. 2014;7:2053–9.
51. Rettig E, Kiess AP, Fakhey C. The role of sexual behavior in head and neck cancer: Implications for Prevention and Therapy. *Expert Rev Anticancer Ther*. 2015;15(1):35–49.
52. Becker-Schiebe M, Sperling M, Pinkert U, Hoffmann W. Impact of p16 alterations and pretreatment anemia on toxicity in head and neck cancer patients undergoing definitive radiochemotherapy. *Oncol Res Treat*. 2015;38(11):570–6.
53. Kian Ang K, Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, et al. Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer. *N Engl J Med* [Internet]. 2010;363(1):24–35. Available from: <http://dx.doi.org/10.1056/NEJMoa0912217>
54. Caro JJ, Salas M, Ward A, Goss G. Anemia as an independent prognostic factor for survival in patients with cancer: a systemic, quantitative review. *Cancer*. 2001;91(12):2214–21.

55. Stadler P, Becker a, Feldmann HJ, Hänsgen G, Dunst J, Würschmidt F, et al. Influence of the hypoxic subvolume on the survival of patients with head and neck cancer. *Int J Radiat Oncol Biol Phys* [Internet]. 1999;44(4):749–54. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18207598>
56. Dunst J. Low hemoglobin levels: Influence on tumor biology and radiotherapy treatment outcome. *Eur J Cancer, Suppl.* 2004;2(2):3–10.
57. Gangopadhyay A, Das J, Nath P, Biswas J. Haemoglobin levels may predict toxicities in patients on pelvic chemoradiation for carcinoma of the cervix — experience of a regional cancer centre. *ecancer.* 2014;8(431):1–8.
58. O'Donovan A, Coleman M, Harris R, Herst P. Prophylaxis and management of acute radiation-induced skin toxicity: A survey of practice across Europe and the USA. *Eur J Cancer Care (Engl).* 2014;24:425–35.
59. Arimura T, Ogino T, Yoshiura T, Toi Y, Kawabata M, Chuman I, et al. Effect of Film Dressing on Acute Radiation Dermatitis Secondary to Proton Beam Therapy. *Int J Radiat Oncol Biol Phys* [Internet]. Elsevier Inc.; 2015;1–5. Available from: <http://dx.doi.org/10.1016/j.ijrobp.2015.10.053%5Cnwww.redjournal.org>
60. Cox J, Stetz J, Pajak TF. Toxicity criteria for Radiation Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer. *Int J Radiat Oncol Biol Phys.* 1995;31:1341–6.
61. Noble-Adams R. Radiation-induced skin reactions. 3: Evaluating the RISRAS. *Br J Nurs* [Internet]. 1999;8(19):1305–12. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10887808>
62. Cork MJ, Danby S. Aqueous cream damages the skin barrier. *Br J Dermatol.* 2011;164(6):1179–80.
63. Tsang M, Guy RH. Effect of Aqueous Cream BP on human stratum corneum invivo. *Br J Dermatol.* 2010;163(5):954–8.
64. Haviland JS, Owen JR, Dewar JA, Agrawal RK, Barrett J, Barrett-Lee PJ, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol* [Internet]. Elsevier Ltd; 2013;14(11):1086–94. Available from: [http://dx.doi.org/10.1016/S1470-2045\(13\)70386-3](http://dx.doi.org/10.1016/S1470-2045(13)70386-3)
65. Rollmann DC, Novotny PJ, Petersen I a., Garces YI, Bauer HJ, Yan ES, et al. Double-Blind, Placebo-Controlled Pilot Study of Processed Ultra Emu Oil Versus Placebo in the Prevention of Radiation Dermatitis. *Int J Radiat Oncol Biol Phys* [Internet]. Elsevier Inc.; 2014;92(3):650–8. Available from: <http://dx.doi.org/10.1016/j.ijrobp.2015.02.028>
66. Cui Z, Xin M, Yin H, Zhang J, Han F. Topical use of olive oil preparation to prevent radiodermatitis: Results of a prospective study in nasopharyngeal carcinoma patients. *Int J Clin Exp Med.* 2015;8(7):11000–6.
67. Chan RJ, Mann J, Tripcony L, Keller J, Cheuk R, Blades R, et al. Natural oil-based emulsion containing allantoin versus aqueous cream for managing radiation-induced skin reactions in patients with cancer: A phase 3, double-blind, randomized, controlled trial. *Int J Radiat Oncol*



- Biol Phys [Internet]. Elsevier Inc; 2014;90(4):756–64. Available from: <http://dx.doi.org/10.1016/j.ijrobp.2014.06.034>
68. Patel a. N, Varma S, Batchelor JM, Lawton P a. Why aqueous cream should not be used in radiotherapy-induced skin reactions. Clin Oncol [Internet]. Elsevier Ltd; 2013;25(4):272. Available from: <http://dx.doi.org/10.1016/j.clon.2012.11.011>
  69. Hindley A, Zain Z, Wood L, Whitehead A, Sanneh A, Barber D, et al. Mometasone furoate cream reduces acute radiation dermatitis in patients receiving breast radiation therapy: Results of a randomized trial. Int J Radiat Oncol Biol Phys [Internet]. Elsevier Inc; 2014;90(4):748–55. Available from: <http://dx.doi.org/10.1016/j.ijrobp.2014.06.033>
  70. Zigmond A, Snaith R. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand. 1983;67(3):361–70.
  71. Finlay A., Khan G. Dermatology and Life Quality Index (DLQI)- a simple practical measure for routine clinical use. Clin Exp Dermatol. 1994;19(3):210–6.
  72. Freedman GM. Topical agents for radiation dermatitis in breast cancer: 50 shades of red or same old, same old? Int J Radiat Oncol Biol Phys [Internet]. Elsevier Inc.; 2014;90(4):736–8. Available from: <http://dx.doi.org/10.1016/j.ijrobp.2014.07.001>
  73. Togni S, Maramaldi G, Bonetta a, Giacomelli L, Di PF. Clinical evaluation of safety and efficacy of Boswellia-based cream for prevention of adjuvant radiotherapy skin damage in mammary carcinoma: a randomized placebo controlled trial. Eur Rev Med Pharmacol Sci. 2015;19(8):1338–44.
  74. Graham P, Browne L, Capp A, Fox C, Graham J, Hollis J, et al. Randomized, paired comparison of No-Sting Barrier Film versus sorbolene cream (10% glycerine) skin care during postmastectomy irradiation. Int J Radiat Oncol Biol Phys. 2004;58(1):241–6.
  75. Manas A, Santolaya M, Ciapa VM, Belinchón B, Tully F. Topical R1 and R2 Prophylactic Treatment of Acute Radiation Dermatitis in Squamous Cell Carcinoma of the Head and Neck and Breast Cancer Patients Treated With Chemoradiotherapy. 2015;210–21.
  76. Zhong WH, Tang QF, Hu LY FH. Mepilex Lite dressings for managing acute radiation dermatitis in nasopharyngeal carcinoma patients: A systematic controlled clinical trial. med oncol. 2013;30(761):1–7.
  77. Bazire L, Fromantin I, Diallo A, De La Lande B, Pernin V, Dendale R, et al. Hydrosorb® versus control (water based spray) in the management of radio-induced skin toxicity: Results of multicentre controlled randomized trial. Radiother Oncol [Internet]. Elsevier Ireland Ltd; 2015;117(2):229–33. Available from: <http://dx.doi.org/10.1016/j.radonc.2015.08.028>
  78. Cox JD, Stetz J. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European organization for research and treatment of cancer (EORTC). Int J Radiat Oncol. 1995;31(5):1341–6.
  79. Baken DM, Woolley C. Validation of the Distress Thermometer, Impact Thermometer and combinations of these in screening for distress. Psychooncology. 2011;20(6):609–14.
  80. Yates JW, Chalmer B, McKegney P. Evaluation of Patients with Advanced Cancer Using the Karnofsky Performance Status. Cancer. 1980;45:2220–4.

81. MacBride SK, Wells ME, Hornsby C, Sharp L, Finnila K, Downie L. A case study to evaluate a new soft silicone dressing, Mepilex Lite, for patients with radiation skin reactions. *Cancer Nurs.* 2008;31(1):E8–14.
82. Trotti A, Colevas AD, Setser A, Rusch V, Jaques D, Budach V, et al. CTCAE v3.0: Development of a comprehensive grading system for the adverse effects of cancer treatment. *Semin Radiat Oncol.* 2003;13(3):176–81.
83. Huang CJ, Hou MF, Luo KH, Wei SY, Huang MY, Su SJ, et al. RTOG, CTCAE and WHO criteria for acute radiation dermatitis correlate with cutaneous blood flow measurements. *Breast* [Internet]. Elsevier Ltd; 2015;24(3):230–6. Available from: <http://dx.doi.org/10.1016/j.breast.2015.01.008>
84. Akizuki N, Yamawaki S, Akechi T, Nakano T, Uchitomi Y. Development of an Impact Thermometer for use in combination with the Distress Thermometer as a brief screening tool for adjustment disorders and/or major depression in cancer patients. *J Pain Symptom Manage.* 2005;29(1):91–9.
85. Fitzpatrick T. The validity and practicality of sun reactive skin types I through IV. *Arch Dermatol.* 1975;124:869–71.
86. Jacobsen PB, Ph D, Donovan KA, Ph D, Trask PC, Ph D, et al. Screening for Psychologic Distress in Ambulatory Cancer Patients A Multicenter Evaluation of the Distress Thermometer. *Cancer.* 2005;103(February):1494–502.
87. Rippon M, White R, Davies P. Skin adhesives and their role in wound dressings. *Wounds UK.* 2007;3(4):76–86.
88. Chelimo C, Elwood JM. Sociodemographic differences in the incidence of oropharyngeal and oral cavity squamous cell cancers in New Zealand. *Aust N Z J Public Health* [Internet]. 2015;39(2):162–7. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25827186>
89. Denham JW, Hamilton CS, Simpson SA, Ostwald PM, O’Brien M, Kron T, et al. Factors influencing the degree of erythematous skin reactions in humans. *Radiother Oncol.* 1995;36(2):107–20.
90. Givens DJ, Karnell LH, Gupta AK, Clamon GH, Pagedar NA, Chang KE, et al. Adverse events associated with concurrent chemoradiation therapy in patients with head and neck cancer. *Arch Otolaryngol head neck Surg.* 2009;135(12):1209–17.
91. Sutherland, Annie E, Bennett NC, Herst PM. Psychological stress affects the severity of radiation-induced acute skin reactions in breast cancer patients. *Eur J Cancer Care (Engl).* Manuscript under review.
92. Schnur JB, Ouellette SC, Dilorenzo T a, Green S, Montgomery GH. A qualitative analysis of acute skin toxicity among breast cancer radiotherapy patients. 2011;268(March 2010):260–8.

## Appendix A: Recent trials investigating the prevention of radiation-induced skin reactions

Reference	Cohort	randomised	blinded	Skin dose measured	Measure	Follow up	Intervention	control	result	P values
Herst 2014	34 breast 36 chest wall	Intra-patient	no	yes	RISRAS RTOG 3x a week	4 weeks	Mepitel Film	Aqueous Cream	90% decrease in RISRAS No moist desquamation under film, 26% under aqueous cream	P<0.001
Rollman 2015	45 breast+chest wall	Inter-patient	yes	no	CTCAE, STAT, Skindex	6 weeks	Emu oil	Cottonseed oil	Patients with emu oil seemed to have slightly worse CTCAE scores, SKindex scores tended to be lower in emu oil patients	P=0.29 for Skindex, not significant for CTCAE
Arimura 2015	271 prostate	none	no	no	'Acute radiation dermatitis' but did not mention how it was scored	4 weeks	Airwall tape	multiple	Difference in development of grade 2 and 3 reactions between intervention and control group (21 and 0 vs 57 and 4)	P<0.001.
Cui 2015	94 nasopharynx	Inter-patient	single	no	VAS and RTOG	2 weeks	Olive oil	Water	Grades I and II occurred in 93.6% of intervention group and 72.3% of control group. Grade III occurred in 6.4% and 27.7%	P<0.01
Palatty 2014	50 head and neck	Inter-patient	single	no	RTOG	2 weeks	Turmeric and sandalwood oil cream	Baby oil	Reduction in all grades of dermatitis at all time points. Grade III was lower in the intervention group, recued dermatitis at 2 week f/u	P<0.015, p<0.001, p<0.01, P=0.015.

Chan 2014	174 total 89 breast 20 lung 65 head and neck	Inter-patient	double	no	CTCAE	4 weeks	Allantoin	Aqueous cream	Aqueous cream seemed to reduce skin reactions compared to intervention. Skin toxicity similar between groups	P=0.56
Hindley 2014	120 breast	interpatient	no	no	Modified RTOG, diaston reflectance spectrometer, HAD and DLQI	2 weeks	Mometasone furoate	Diprobace	Mean RTOG scores less for intervention, Max and mean erythema scores were also less	P=0.046, 0.018, 0.12
Togni 2015	114 breast	Inter-patient	no	no	RTOG and photoshop	none	Boswellia cream	Base cream	Mean value of skinn damage using photo shop was lower in the Boswellia group, however RTOG scores did not reach statistical significance	P=0.009, 0.066
Manas 2015	19 head and neck 79 breast	Inter-patient	no	no	CTC	2 weeks	R1 and 2 cream (water based gel and lactokine lotion)	5% wt/wt urea lotion	R1 and 2 reduced the grade of dermatitis. At 2 week f/u, 66.7% had no dermatitis compared to 34% in the control group	P=0.003

## Appendix B: Recent trials investigating the management of acute radiation dermatitis.

Reference	Cohort	randomised	blinded	Skin dose measured	Measure	Follow up	Intervention	control	result	P values
Paterson 2012	80 chestwall	Intra-patient	no	yes	RISRAS	Until all skin reactions had resolved (usually 4-5 weeks after treatment)	Mepilex Lite	Aqueous Cream	Mepilex Lite dressings did not reduce the incidence of moist desquamation but did reduce the overall severity of skin reactions by 41%	P<0.001
Zhong 2013	88 nasopharynx	Inter-patient	no	no	RISRAS, VAS	Complete skin integrity of all wounds	Mepilex Lite	saline	Dermatitis healed faster Mepilex group than the control group (median 16 vs 23 days)	P=0.009
Bazire 2015	278 breast	Inter-patient	no	no	colourimetry	Last assessment at 28 days from enrolment	Hydrosorb	Water based spray	This study did not demonstrate any significant difference between Hydrosorb and placebo for the treatment of grade 1 and 2 radiation dermatitis.	P=0.36

## Appendix C: Participant information sheet

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*Te Whare Wānanga o Otago*

### PARTICIPANT INFORMATION SHEET

<b>Study title:</b>	<b>Skin Reactions during Radiation Therapy</b>	
<b>Principal investigator:</b>	Name: Dr Ptries Herst  Department: Radiation Therapy (UOW)  Position: Senior lecturer	Contact phone number  027-3483945

You are invited to take part in a clinical trial. A clinical trial is a type of research study. Please read the information in this form carefully; it tells you why we want to do the trial and what it means for you to take part. The research radiation therapist will talk to you about the trial and will be able to answer any questions you may have about it or your involvement. Please feel free to discuss your participation in this trial with family, whanau and friends and take your time to decide whether you would like to take part. All participation in this study is entirely voluntary (your choice) and even if you decide to take part now and change your mind later, you are free to withdraw at any time. Whether you decide to participate in the study or not, your current or future healthcare will not be affected in any way.

If you decide to take part in the study, you will be asked to sign the pages at the end of this form to show that you have agreed to take part. You will be given a copy of the participant information sheet and consent form to take home with you.

Thank you for taking the time to read this information sheet.

### **1. Why are we doing this study?**

*This study compares the effect of Mepitel Film with that of a conventional moisturising cream on skin side effects in patients receiving radiation therapy for head and neck cancer.*

You have been invited to take part in this study because you have been diagnosed with head and neck cancer and are about to undergo radiation treatment at Christchurch Hospital. Radiation therapy is given with the aim of getting rid of all cancer cells in the area. Irradiation often causes skin reactions (side effects), which can vary from a slight reddening skin to severe redness and itching (which is comparable to sunburned skin). In some cases the skin may peel away in places, leaving the underlying tissues exposed. There is no standard way to prevent the skin reacting like this to radiation therapy.

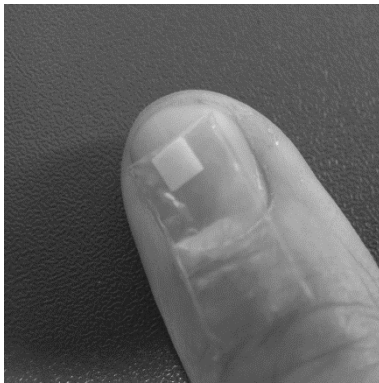
We have already done three skin trials in New Zealand that compared soft silicone dressings with moisturising cream in breast cancer patients. We found that the dressings reduced the severity of the skin reactions. Our latest study showed that when a very thin transparent (see-through) silicone film is applied to breast skin on the first day of treatment, severe skin reactions can be avoided. However, it is not always practical to apply the film to the entire area of skin that will be irradiated. In this study we want to wait until the skin turns a very faint pink before applying the dressing. This silicone film has not been trialled in head and neck cancer patients until now.

### **2. Who will be asked to participate in this study?**

All patients who come to the department to receive radiation therapy for squamous cell carcinoma of the head and neck region will be approached with information about the study by the research radiation therapist. However patients who have had previous radiation therapy to the head and neck area, who have metastatic disease (spread beyond the neck region), who have facial hair in the treatment region, who have a K score of <70, or who are not able to attend the follow up visits after completion of treatment will NOT be able to participate in the trial.

### **3. What does my participation in the study involve?**

- Once you have been accepted into the trial and you have signed the consent form, the research radiation therapist will do an initial assessment of your skin to tell us what your skin looks like before you start radiation treatment. You will also be asked information general information about your health that may affect your likelihood of getting severe skin reactions during your radiation treatment.
- Baseline photos will be taken of the skin in the H&N area. Semi-permanent marker pens will be used to indicate which skin area will be covered in Film and which will be treated with sorbolene cream and photographs will be taken of these areas. Additional photographs **may** be taken in case you have a severe skin reaction. Parts of these photos may be used, **with your permission**, for reporting or publication purposes. You will not be able to be identified in any of these photographs.
- During the first few weeks of your treatment, we will measure how much radiation your skin receives each day. We will do this by placing small flat squares directly on your skin (see Figure 1 below). These small squares contain special equipment that measures the exact amount of radiation received by your skin during each treatment.



**Figure 1:** A small white square on this finger nail is called a dosimeter and squares like this will be placed on your skin to measure how much radiation your skin receives each day.

- You will be seen three times a week by the research radiation therapist, who will check your skin to see if there is any reaction to the radiation treatment and who will record these findings on an assessment form. The assessment form consists of a researcher part which will be filled in by the research radiation therapist and a patient part which you will be asked to fill in. This part will ask you to compare how comfortable your skin feels underneath the film and underneath the cream.
- Based on your initial planning scan, an area of your skin that will get the highest dose will be selected as the trial area. This area of your skin will be divided into two halves. One half will be covered in film by the research radiation therapist, whilst we will ask you to put moisturising cream twice a day on the other half.
- After you finish your course of radiation therapy we ask you to come back to the department once a week until your final check-up four weeks later (which is part of your normal hospital care) so we can keep checking your skin and recording the severity of any skin reactions you may develop once you finish your radiation treatment.



- Once a week you will also be asked to fill out a brief questionnaire (the cancer distress thermometer) about how stressed you feel before, during and after your radiation therapy treatment.
- After you have completed this trial we will ask you to fill out a brief questionnaire that will ask you about your experiences of being on the trial and using the Mepitel Film.

#### **4. Are there any risks to me if I participate in this study?**

- Our experience with the film has shown us that it is very comfortable to wear and makes the skin reactions less severe.
- In the unlikely event of an adverse reaction to the film we will ask you to stop using it and treat the affected skin with a moisturising cream instead.
- In the unlikely event of a physical injury as a result of your participation in this study, you may be covered by ACC under the Injury Prevention, Rehabilitation and Compensation Act. ACC cover is not automatic and your case will need to be assessed by ACC according to the provisions of the 2002 Injury Prevention Rehabilitation and Compensation Act. If your claim is accepted by ACC, you still might not get any compensation. This depends on a number of factors such as whether you are an earner or non-earner. ACC usually provides only partial reimbursement of costs and expenses and there may be no lump sum compensation payable. There is no cover for mental injury unless it is a result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigators. If you have any questions about ACC, contact your nearest ACC office or the investigator.

#### **5. Are there any costs involved if I participate in this study?**

There are no costs associated with this trial. You will be reimbursed for any follow up sessions that are not part of standard care (up to \$25 per visit).

#### **6. What will you do with the information?**

Information that may identify you, such as your name, address and date of birth, will be kept together with your medical records, skin reactions and exit questionnaire in your patient file in the oncology department.

The Principal Investigator, Dr Patries Herst, will collate and analyse all the information. She will receive your information in a form that is no longer linked to your name, address or date of birth. You will be given a special trial number to which all the trial information is linked.

This de-identified information will be stored in a locked metal filing cabinet in the office of the Principal Investigator, Dr Patries Herst, at the University of Otago, Wellington for a period of 10 years. Only the research radiation therapist will be able to link the de-identified information to you personally.

When the study is completed the principal investigator, Dr Patries Herst will collate and analyse the information from all the participants of the study. This will tell us whether the film is better than the cream in managing skin reactions. If this is the case, we aim to conduct a larger trial, and we would like to incorporate the data from this trial into a larger future study.

We anticipate that this will lead to a standardized treatment for radiation-induced skin reactions for head and neck cancer patients.

### **Reporting**

- We will report on the results of this study in scientific reports and publications.
- If you so wish, you can be informed of the results of the study by a letter written in lay terms from the Principal Investigator, Dr Patries Herst

**NO material will be published which can identify you personally.**

You may be asked if we can use photos of parts of your skin to illustrate our findings. You will in no way be able to be identified by these photos.

### **7. Do I have to participate in this study?**

No, there is absolutely no requirement to participate in the study.

### **8. Can I withdraw from the study if I change my mind?**

If you decide to take part in the study now and change your mind later, you are free to withdraw from the study at any time. Whether you decide to participate in the study or not will not affect your current or future healthcare in any way.

If you wish to withdraw, please advise the research radiation therapist. We will keep the information we have collected about you for our analysis. However, if you request it, all information and data that have been collected about you will be completely deleted from the database.

#### **9. What if I have more questions or concerns about this study?**

If you have any questions or concerns about your rights as a participant in this research study you can contact an independent health and disability advocate. This is a free service provided under the Health and Disability Commissioner Act. Local (03) 479 0265; Telephone: (NZ wide) 0800 555 050; Free Fax (NZ wide): 0800 2787 7678 (0800 2 SUPPORT); Email (NZ wide): [advocacy@hdc.org.nz](mailto:advocacy@hdc.org.nz). If there is a specific Māori issue/concern please contact Linda Grennell at 0800 37 77 661.

**If you have any questions or concerns about your skin reactions or any other aspects of this study, at any time, please call the Research Radiation Therapist: Hayley Wooding phone: 3640020 ext 88487**

This study has been approved by the University of Otago Human Ethics Committee (trial number H14/111). If you have any concerns about the ethical conduct of the research you may contact the Committee through the Human Ethics Committee Administrator (ph 03 479 8256). Any issues you raise will be treated in confidence and investigated and you will be informed of the outcome.

## Appendix D: Informed Consent



### INFORMED CONSENT

#### Skin Reactions during Radiation Therapy

**Principle investigator:** Dr Ptries Herst ([ptries.herst@otago.ac.nz](mailto:ptries.herst@otago.ac.nz);  
mobile: 027-3483945)

**Name of Participant .....**

1. I have read and I understand the information sheet dated September 2015 for volunteers taking part in the study designed to investigate whether Mepitel Film decreases the severity of skin reactions caused by radiation therapy.
2. I have had the opportunity and time to discuss this study with family, whanau and friends. I am satisfied with the answers I have been given.
3. I understand that taking part in this study is completely voluntary (my choice), and that I may withdraw from the study at any time, without giving a reason and this will in no way affect my future health care.
4. I understand that my participation in this study is confidential and that no material that could identify me will be used in any reports on this study.
5. I understand that the film will be removed if I have a reaction to it.
6. I know who to contact if I have any questions about the study.
7. As a participant I agree to:

- Regular skin reaction assessments by the research radiation therapist, which will be carried out three times a week during treatment as well as once a week after the completion of treatment until the final check-up four weeks after treatment. The skin assessment form has a patient part to be filled in by myself and a researcher part to be filled in by the research radiation therapist.
- Use of photographs that may be taken of parts of my skin for publication purposes as long as I cannot be identified from these photos.
- Filling in the distress thermometer questionnaire once a week during the study.
- Filling in an exit questionnaire at the end of the study that will allow me to describe my experiences in taking part in this trial and using the film on my skin.

**I consider my ethnicity to be:**

☐ New Zealand European

☐ Māori

☐ Samoan

☐ Cook Islands Maori

☐ Tongan

☐ Niuean

☐ Chinese

☐ Indian

☐ Other (such as Dutch, Japanese, Tokelauan). Please state.

I, ..... (*full name*) hereby consent to  
take part in this study.

Date:

Signature:

Full names of researchers:

Hayley Wooding, Dr Iain Ward

Contact phone number for  
researchers:

3640020 ext. 88487

Project explained by:

Treating physician:

Signature:

Date:

This study has been approved by the University of Otago Human Ethics Committee. If you have any concerns about the ethical conduct of the research you may contact the Committee through the Human Ethics Committee Administrator (ph 03 479 8256). Any issues you raise will be treated in confidence and investigated and you will be informed of the outcome.

## Appendix E: Randomisation sheet

### Randomisation coversheet

#### Effect of Mepitel Film on skin reaction severity in Head and Neck cancer patients

Date:

To: Ptries Herst

Email: [ptries.herst@otago.ac.nz](mailto:ptries.herst@otago.ac.nz)

Phone: 04 385 5475

From:

Email:

Phone:

### Randomisation Dunedin/Christchurch

Patient initials:

Patient DoB:

Gender:

Chemo/RT      RT alone

Mepitel Film:      Superior/Lateral:

Inferior/Medial:

Patient randomisation number:

Randomisation date:

Randomisation completed by:

Signature

## Appendix F: Skin care guidelines

### 1.1 Acute Radiation Therapy Skin Reactions: Guidelines for Management

#### 1.2 Purpose/Objective

Management of acute radiation skin reactions is systematic, evidence-based and multi-disciplinary in approach

#### 1.3 Personnel Authorised to Perform Procedure

Radiation Therapists - for patients who have been assessed to have reactions in the categories of erythema and dry desquamation

Registered Nurses – assess, plan and deliver care for patients with reactions in the categories of erythema, dry desquamation, moist desquamation or necrosis

Enrolled Nurses may deliver care planned and supervised by Registered Nurses or Medical Practitioners

#### 1.4 Associated Documents

Acute Radiation Therapy Skin Reaction Policy

On Treatment Review Protocol

Patient Education Protocol

#### 1.4 Definitions

The four main categories of acute radiation-induced skin reactions are as follows (Naylor & Mallett 2001:223). All skin assessment is based on these categories:

Category	Description
Erythema	Reddened skin, which may be oedematous and feel hot and irritable
Dry desquamation	Dry, flaky or peeling skin that may be itchy
Moist desquamation	Peeling skin with exposure of the dermis and exudate production, often painful and may become infected
Necrosis	Death of tissue, skin may darken and turn black

#### 1.5 Assessment Tool

The CTCAE v 4.0 is used to assess symptom toxicity.

#### 1.6 Guideline

This framework is based on current best-practice evidence. Outcomes to be achieved are:

- ☐ To ensure and enable best supportive care of patients undergoing radiation treatment, acknowledging information and education needs of patients and carers
- ☐ Identify risk factors for acute radiation skin reactions occurring
- ☐ Promote principles of optimum wound healing, minimising the risk of infection



☐ To ensure continuity across acute/community settings

Step	Action
1	<p><b>Assessment:</b></p> <ul style="list-style-type: none"> <li>☐ To be undertaken prior to, during and post radiation treatment on an ongoing basis by health-care professionals who have knowledge and understanding of the principles and practice of radiation skin care management. Toxicity is graded weekly by the Radiation Oncologist using the CTCAE v4.0.</li> <li>☐ This should include actual and potential risk factors including:             <ul style="list-style-type: none"> <li>☐ fractionation</li> <li>☐ concomitant techniques</li> <li>☐ radiation energy and type</li> <li>☐ treatment technique</li> <li>☐ volume and dose of radiation</li> <li>☐ nutritional status</li> <li>☐ use of radio-sensitising drugs</li> <li>☐ area receiving radiation</li> <li>☐ current skin condition</li> <li>☐ areas of skin already exposed to trauma: surgery, skin disorders</li> <li>☐ patient factors – immobility, work environment, limited self care ability, age, medical conditions.</li> <li>☐ identification of information needs of patients and/or carers</li> <li>☐ identification and documentation of changes in skin condition</li> </ul> </li> </ul>
2	<p><b>Implementation</b></p> <p>The process of implementation includes:</p> <ul style="list-style-type: none"> <li>☐ clear, consistent written and verbal information available for patients and care-givers</li> <li>☐ care planned within a multi-disciplinary context. This includes as appropriate: dietitian, occupational therapist, speech-language therapist, physiotherapist, wound care nurse specialist</li> <li>☐ ongoing needs of patients and care-givers during treatment and rehabilitation are acknowledged</li> </ul>
3	<p><b>General Skin Care Advice</b></p> <p>The following information must be available in written form for patients and carers:</p> <ul style="list-style-type: none"> <li>☐ skin in the radiation treatment area may be washed with warm water, using non-perfumed non-alkaline or pH neutral soaps or shampoos for washing e.g. Dove®.</li> <li>☐ deodorant may be used</li> <li>☐ pat the area dry, avoid rubbing</li> <li>☐ wear loose clothes made from natural fibres</li> <li>☐ shaving should be avoided within the radiation therapy field. If absolutely necessary use of an electric razor is recommended</li> <li>☐ skin should be protected from extremes of temperature</li> <li>☐ avoid sunscreen in the treatment area. Sunscreen (factor 30+) should be used on all other exposed skin and remain continuous throughout life.</li> <li>☐ FattyE Cream may be used for comfort if erythema or dry desquamation present. Not to be used on broken skin.</li> <li>☐ Aloe Vera has no proven benefit in radiation skin reactions but may be used if patient wishes</li> <li>☐ saline baths or soaks can be used as required (remove soaks before they dry out)</li> <li>☐ take care to preserve skin markings</li> <li>☐ avoid alcohol based products and the use of powders</li> <li>☐ using tape to secure dressings within the treatment field should be avoided</li> <li>☐ if reaction occurs patients should seek advice regarding swimming in chlorinated water</li> <li>☐ Patient Information Sheets on skincare are available on 'G' drive under Common/Patient Information/Radiation/RT NP education.</li> </ul>

4	<p><b>Erythema</b></p> <p>The development of a pink-red area 2-3 weeks into radiation treatment may occur. This is caused by the release of histamine-like substances from damaged dermal cells, leading to dermal oedema, erythrocyte extravasation and dilation of capillaries. Leading to the various shades of skin redness.</p> <ul style="list-style-type: none"> <li>Refer to General Skin Care Advice for management</li> </ul> <p><b>Transient Erythema</b></p> <p>The development of a pink-red area which occurs with the first or second dose of radiation being given. This reduces within a matter of hours to days within commencing treatment.</p> <ul style="list-style-type: none"> <li>Reassure patient this is an initial temporary reaction</li> </ul> <p><b>Dry desquamation</b></p> <p>The basal cells injured at the beginning of treatment continue their normal upward progression through the epithelium, reach the corneocytic stage, become cornified and shed. If the basal layer has been repaired before desquamation, the skin surface remains dry.</p> <p>Patients may complain of discomfort, burning or itching. They may also experience superficial flaking of the epidermis.</p> <p>Principles of management include:</p> <ul style="list-style-type: none"> <li>regular assessment and documentation by health-care professional, daily for inpatients and on treatment days for patients receiving treatment</li> <li>continue with general skin care management</li> <li>moisturise the area 2-3 times a day with FattyE cream or similar, avoiding macerated skin.</li> <li>water soaked gauze applied for 10-15 minutes as required may be soothing for heat and itchiness</li> <li>decrease friction if this is an issue by applying barrier protection which can be removed easily for treatment e.g. Mepilex lite</li> <li>hydrocortisone 1% may be considered by medical staff for itchy skin if unrelieved by other measures. Apply sparingly BD-TDS. Not on broken or infected areas. May delay healing time and affect skin integrity if used long term.</li> <li>Grade 1 erythema may be treated with a thin application of Cavilon™</li> </ul>
5	<p><b>Moist desquamation</b></p> <p>Loss of the epidermis resulting in exposure of the dermis with associated exudate production, pain and risk of infection.</p> <p>Principles of management include:</p> <ul style="list-style-type: none"> <li>regular assessment and documentation by health-care professional, daily for inpatients and on treatment days for patients receiving treatment</li> <li>a moist wound healing environment</li> <li>assessment of analgesic requirements for dressing</li> <li>cleansing as required using tepid normal saline, saline soaks used as required may be soothing</li> <li>During treatment:             <ul style="list-style-type: none"> <li>Light to moderate exudating reaction sites:                 <ul style="list-style-type: none"> <li>Cover with a low adherent dressing (e.g. Jelonet/ Adaptic/ Mepilex transfer™) and secondary dressing such as gamgee secured with tubifast</li> <li>Remove before treatment and reapply after daily treatment.</li> </ul> </li> <li>Consider use of Cuticerin/Jelonet or similar and combine or similar secured with tubifast® as a primary dressing for moderate-heavy exudating reaction sites.</li> <li>Application of dressings intended to stay in place during treatment need to be discussed with the Radiation Oncologist or Radiation Therapist, prior to use.</li> </ul> </li> </ul>

6	<ul style="list-style-type: none"> <li>At completion of treatment –</li> </ul> <p>Continue with dressing regimen working in reverse as skin heals with regular review by a health care professional at follow-up or in the community</p> <p><b>Infected Wounds</b></p> <p>Infection is characterised by the presence of redness, pain, swelling, heat, odour and exudate. Principles of Management include:</p> <ul style="list-style-type: none"> <li>assessment of analgesia requirements for dressing change</li> <li>identifying type of wound infection, obtain swab and send for micro/culture + sensitivity</li> <li>cleansing as required with warmed normal saline</li> <li>assessing level of exudate and choosing appropriate wound product to contain exudate</li> <li>assessing odour level, consider use of activated charcoal dressings. Essential oils e.g. tea tree or eucalyptus, may be applied to outside of dressing if acceptable to patient</li> </ul> <p>Consider use of topical or systemic antibacterial agents dependent on result of swab. These may include Metronidazole gel, silver based agents or iodine based agents. Application of these products is done in consultation with Wound Care Clinical Nurse Specialist and Radiation Oncology Team.</p> <p>Wound would be cleaned prior to radiation treatment with use of these products and reapplied post treatment</p> <ul style="list-style-type: none"> <li>Silver based products are not to be used during treatment period but may be considered on treatment completion</li> </ul>
7	<p><b>Fungating Wounds</b></p> <p>Malignant fungating wounds arise when cancer cells infiltrate and proliferate within the skin resulting in the development of nodular and/or ulcerating wounds (Naylor, 2005)</p> <p>Symptoms to consider with fungating wounds include malodour, exudate, pain, bleeding and psychosocial aspects for the patient</p> <p>Principles of Management include:</p> <ul style="list-style-type: none"> <li>assessing psycho-social impact on patient and family. Refer to appropriate multidisciplinary team member as required</li> <li>identifying and treating infection which may contribute to malodour – obtain swab for micro/culture + sensitivity, topical or systemic treatment as needed</li> <li>assessing pain levels and analgesia requirements for dressings</li> <li>assessing and treating odour:             <ul style="list-style-type: none"> <li>treat infection if odour causing</li> <li>consider use of dressings with activated charcoal to absorb odour or use of essential oils</li> </ul> </li> </ul> <p>Exudate</p> <ul style="list-style-type: none"> <li>Low - consider a thin hydro gel remove prior to treatment</li> <li>Moderate – consider Allevyn™, or Mepilex Lite™</li> <li>Heavy - consider Combine, Mesorb/Mepilex Transfer/Mepitel™</li> <li>If extremely heavy consider wound drainage bags or disposable pads</li> </ul>

	<ul style="list-style-type: none"> <li>❑ Bleeding – may be very little or large <ul style="list-style-type: none"> <li>o consider haemostatic dressings e.g. alginates – Kaltostat, Seasorb or similar, for small amounts.</li> <li>o large amounts can be life threatening, apply pressure and obtain help.</li> </ul> </li> <li>❑ If persistent bleeding, consider complete blood count to monitor parameters as may affect radiation effectiveness</li> <li>❑ Necrosis requires input from the Wound Care Nurse Specialist, Plastics team or General Surgery.</li> <li>❑ Remove dressings prior to radiation treatment and reapply post treatment</li> </ul>
8	<p><b>Follow up</b></p> <p>While on treatment out-patients will be reviewed every treatment day by the radiation therapist and nursing staff</p> <p>In-patients will be reviewed by the ward nurse in consultation with oncology inpatient CNS. Radiation oncology nurses may be contacted on 89504 for advice if needed.</p> <p>On completion of treatment a community referral should be made, if required, with specific care instructions (wound care card) to the district nurse on the care needed.</p>

## References

- Bolderston, A., Lloyd, N. S., Wong, R. K. S., Holden, L., Robb-Blenderman, L. Ontario Cancer Care Supportive Guidelines Group. The Prevention and Management of Acute Skin Reactions Related to Radiation Therapy. Practice Guideline Report #13-7. [http://www.cancercare.on.ca/access\\_PEBBC.htm](http://www.cancercare.on.ca/access_PEBBC.htm)
- Draelos, Z. D. (2012). New treatments for restoring impaired epidermal barrier permeability: Skin barrier repair creams. *Clinics in Dermatology* 30(3), 345-348.
- Mc Question, M. (2006). Evidence-Based Skin Care Management in Radiation Therapy. *Seminars in Oncology Nursing*, 22(3), 163-173.
- Mc Question, M. (2011). Evidence-Based Skin Care Management in Radiation Therapy: Clinical Update. *Seminars in Oncology Nursing*, 27(2), e1-e17.
- Noble-Adams, R. (1999). Radiation-induced reactions 1: an examination of the phenomenon. *British Journal of Nursing*. 8(17), 1134-1140.
- Naylor, W. (2005). Guidelines for Wound Management in Palliative Care. Mercy Hospice, Auckland. Naylor, W., Lavery, D., & Mallett, J. (2001). *Handbook of Wound Management in Cancer Care*. Blackwell Science, London.
- Wells, M., & MacBride, S. (2003). Radiation Skin Reactions. In S. Faithful & M. Wells (Eds) *Supportive Care in Radiotherapy* p135-159. Churchill Livingstone.

## Appendix G: NZ validated distress thermometer

### Cancer Related Distress Screen

Please circle the number (0-10) that best describes how much distress (mamae) you have been experiencing in the past week including today

**Extreme Distress**

**Moderate Distress**

**No Distress**

Please circle the number (0-10) that best describes how much impact this distress (mamae) has had on your life.

**Extreme Impact**

**Moderate Impact**

**No Impact**

Please indicate if any of the following has been a problem for you in the past week including today. Be sure to check Yes or No for each.

Yes	No	Spiritual (Wairua) Concerns	Yes	No	Physical (Tinana) Problems
<input type="checkbox"/>	<input type="checkbox"/>		<input type="checkbox"/>	<input type="checkbox"/>	Appearance
		<b>Practical Problems</b>	<input type="checkbox"/>	<input type="checkbox"/>	Bathing/Dressing
<input type="checkbox"/>	<input type="checkbox"/>	Child care	<input type="checkbox"/>	<input type="checkbox"/>	Breathing
<input type="checkbox"/>	<input type="checkbox"/>	Housing	<input type="checkbox"/>	<input type="checkbox"/>	Changes in urination
<input type="checkbox"/>	<input type="checkbox"/>	Financial	<input type="checkbox"/>	<input type="checkbox"/>	Constipation
<input type="checkbox"/>	<input type="checkbox"/>	Transportation	<input type="checkbox"/>	<input type="checkbox"/>	Diarrhoea
<input type="checkbox"/>	<input type="checkbox"/>	Work / school	<input type="checkbox"/>	<input type="checkbox"/>	Eating
<input type="checkbox"/>	<input type="checkbox"/>	Cultural obligations	<input type="checkbox"/>	<input type="checkbox"/>	Fatigue
<input type="checkbox"/>	<input type="checkbox"/>	Hospital Processes	<input type="checkbox"/>	<input type="checkbox"/>	Feeling Swollen
			<input type="checkbox"/>	<input type="checkbox"/>	Fevers
		<b>Family (Whanau) Problems</b>	<input type="checkbox"/>	<input type="checkbox"/>	Getting around
<input type="checkbox"/>	<input type="checkbox"/>	Dealing with children	<input type="checkbox"/>	<input type="checkbox"/>	Indigestion
<input type="checkbox"/>	<input type="checkbox"/>	Dealing with partner	<input type="checkbox"/>	<input type="checkbox"/>	Memory/concentration
<input type="checkbox"/>	<input type="checkbox"/>	Other family members	<input type="checkbox"/>	<input type="checkbox"/>	Mouth sores
		Family/Whanau dealing with the situation	<input type="checkbox"/>	<input type="checkbox"/>	Nausea
			<input type="checkbox"/>	<input type="checkbox"/>	Nose dry / congested
		<b>Emotional (Hinengaro) Problems</b>	<input type="checkbox"/>	<input type="checkbox"/>	Pain
<input type="checkbox"/>	<input type="checkbox"/>	Depression	<input type="checkbox"/>	<input type="checkbox"/>	Sexual
<input type="checkbox"/>	<input type="checkbox"/>	Fears	<input type="checkbox"/>	<input type="checkbox"/>	Skin dry / itchy
<input type="checkbox"/>	<input type="checkbox"/>	Anxiety	<input type="checkbox"/>	<input type="checkbox"/>	Sleep
<input type="checkbox"/>	<input type="checkbox"/>	Sadness	<input type="checkbox"/>	<input type="checkbox"/>	Tingling in hands /feet
<input type="checkbox"/>	<input type="checkbox"/>	Worry			
<input type="checkbox"/>	<input type="checkbox"/>	Loss of interest in usual activities			
			<b>Other Problems</b>		
			_____		
			_____		
			_____		

**Appendix H: Exit Questionnaire****Mepitel Film Exit Questionnaire**

1. Was taking part in this trial a positive experience for you?

Yes/No

Please comment in the box below:

2. Do you think that the dressings were better than the cream in managing your skin reactions?

Yes/No

Please comment in the box below:

3. What were the advantages of the Mepitel Film dressings for you?  
(eg ease of use, comfort, symptom relief and everyday use)

4. What were the disadvantages of the Mepitel Film dressings for you?  
(eg ease of use, comfort, symptom relief and everyday use)

5. Based on your experience with this trial, would you take part in other clinical trials when appropriate?

Yes/No

Please comment in the box below:



6. Would you like the results of this trial sent to you? Yes/No

Thank you for taking part in this trial. This valuable research would not be possible without your help.

Best of wishes for the future.

## Appendix I: Fitzpatrick Skin type assessment

Fitzpatrick skin-type chart

Patient no:

Randomisation:

### Genetic disposition

	0	1	2	3	4
<b>Eye colour</b>	Light blue Light grey Light green	Blue Grey Green	Blue	Dark brown	Brownish Black
<b>Hair colour</b>	Sandy red	Blonde	Lt brown Dark blonde	Dark brown	Black
<b>Skin colour</b>	Reddish	Very pale	Pale Beige tint	Light brown	Dark brown
<b>Freckles</b>	Many	Several	Few	Incidental	None

Total score =

### Reaction to sun exposure

	0	1	2	3	4
<b>Too much sun?</b>	Sore, red, blister, peel	Blister then peel	Burn sometimes then peel	Rarely burn	Never burn
<b>Turn brown?</b>	Not at all	Light colour tan	Reasonable tan	Tan very easily	Turn dark brown quickly
<b>Turn brown within several hours?</b>	Never	Seldom	Sometimes	Often	Always
<b>Reaction of face to sun</b>	V. sensitive	Sensitive	Normal	Very resistant	Never had a problem

Total score =

**Tanning habits**

	0	1	2	3	4
<b>Last exposed to sun (or sunbed)?</b>	>3 months ago	2-3 months ago	1-2 months ago	<1 month ago	<2 weeks ago
<b>Last exposed area to be treated?</b>	Never	Hardly ever	Sometimes	Often	Always

Total score =

**Fitzpatrick Skin type score**

0-7	I	Highly sensitive - always burns - never tans
8-16	II	Very sun sensitive - burns easily - tans minimally
17-25	III	Sun sensitive skin - sometimes burns - slowly tans light brown
26-30	IV	Minimally sun sensitive - burns minimally - tans mid brown
>30	V-VI	Sun insensitive skin - rarely/never burns - deeply pigmented